COMPARISON OF AEROBIC EXERCISE INTENSITY PRESCRIPTION METHODS IN BREAST CANCER PATIENTS AND SURVIVORS

by

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Abstract

It is accepted that exercise plays a significant role in breast cancer rehabilitation, but there has been limited emphasis on control and measurement of the intensity of exercise in cancer research. It is unknown how intensities achieved by different methods of intensity prescription compare, which complicates the interpretation and comparison of studies. The accuracy of these methods in achieving the prescribed intensity is also unknown; and methods that are inaccurate could be unsafe or ineffective in this population. Therefore, a cross-sectional study was performed to compare the achieved intensity and accuracy of four common methods of intensity prescription within and between three post-menopausal groups: breast cancer patients recently finished chemotherapy, survivors finished treatment and healthy controls (N=30). In randomized order, the metabolic equation for walking (MET equation), heart rate reserve (HRR), direct heart rate (direct HR) and rating of perceived exertion (RPE) methods were used to prescribe an intensity of 60% of oxygen consumption reserve (VO_2R) in separate 10-minute bouts, with recovery between bouts. Expired gas analysis was used to measure the intensity achieved during each bout. Accuracy was defined as: [60%VO_2R-achieved intensity]. In ranked order, the average achieved intensity (%VO_2R) and accuracy (percentage points (+/-ppts)) of the methods in the patient group were: HRR: 61%, 3 ppts; MET equation: 56%, 4 ppts; direct HR: 60%, 8 ppts; RPE: 53%, 9 ppts. The HRR method is recommended in this population based on accuracy and feasibility (no expired gas analysis or re-testing required). The MET equation method is also recommended, with re-testing to account for changes in peak oxygen consumption. The direct HR method could be unsafe, as it achieved intensities

much higher than intended (77%), and would be ineffective in research where the effect of exercise is measured, as there was a large range of achieved intensities (42%). In the survivor group results were: MET equation: 59%, 3 ppts; HRR: 63%, 5 ppts; direct HR: 64%, 5 ppts; RPE: 47%, 13 ppts. The top three methods were comparable in accuracy in this group, and appear to be safe and effective, while the RPE method was inaccurate and is not recommended.

Preface

This study involved human subjects, and thus received approval from The Clinical Research Ethics Board of The University of British Columbia (certificate number: H09-03418).

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List of abbreviations

ACSM – American College of Sports Medicine
BMI – Body mass index
CR-10 – Borg's category-ration rating of perceived exertion scale
eMET – estimated maximal metabolic equivalent value
G – grade
HR – heart rate
HR_{actual} – measured maximal heart rate
HR_{max} – maximal heart rate
HR_{pred} – predicted maximal heart rate
HRR – heart rate reserve
HR_{rest} – resting heart rate
kg – kilogram
LVEF - left ventricular ejection fraction
M = mean
m – meters
MET – metabolic equivalent
min – minute
mL – milliliter
mMET - measured maximal metabolic equivalent value
ppts – percentage points
RBC – red blood cell
RMR – resting metabolic rate
RPE – rating of perceived exertion
S – speed
SERM - selective estrogen receptor modulator
THR – target heart rate
TRPE – target rating of perceived exertion
TVO_2 – target volume of oxygen consumption
VO_2 – volume of oxygen consumption
VO_{2max} – maximal volume of oxygen consumption
VO_{2peak} – peak volume of oxygen consumption
VO_{2rest} – resting volume of oxygen consumption
VO_2R – oxygen consumption reserve

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Chapter 1: Introduction

Introduction

Breast cancer is the most common malignancy affecting women around the world (Boyle & Bernard, 2008). In Canadian women alone, an estimated 23,200 new cases of breast cancer will occur in 2010, and a lifetime incidence rate of 1 in 9 is reported (Canadian Cancer Society's Steering Committee, 2009; Canadian Cancer Society's Steering Committee, 2010). The Unites States, Northern Europe and Australia have similar incidence rates to Canada (Canadian Cancer Society/National Cancer Institute of Canada, 2007). Fortunately, the mortality rate for this disease has been steadily declining over the past 10 years, due to increased screening and more effective adjuvant therapies such as chemotherapy and radiation (Canadian Cancer Society/National Cancer Institute of Canada, 2007). This has caused a surge in the number of breast cancer survivors alive today, representing 1% of the Canadian population (Canadian Cancer Society/National Cancer Institute of Canada, 2008), many of whom have a normal life expectancy (Hortobagyi, 2003). As a result of the recent recognition of breast cancer as a manageable or chronic disease, a high priority is the challenge of addressing the sequelae of the disease, including managing treatment side effects, limiting the physical decline commonly observed with treatment, and reducing the risk of other comorbid conditions (Schmitz et al., 2010). Research over the past two decades clearly indicates that exercise plays a significant role in cancer rehabilitation (Schmitz et al., 2010), however, the specifics of the optimal exercise prescription required to maximize beneficial outcomes and minimize risks in this population have yet to be established. While addressing this research gap, it is necessary to take into

account the range of prevalent side effects of breast cancer treatment. In particular, the side effects have a high potential to affect exercise intensity prescription.

Exercise and breast cancer research results

The positive effect of exercise both during and after treatment for women with breast cancer is quite significant. There is an abundance of research indicating that exercise has beneficial effects on some side effects of chemotherapy and/or radiation treatment for breast cancer, such as fatigue (Battaglini, 2004; Campbell, Mutrie, White, McGuire, & Kearney, 2005; Hsieh et al., 2008; Mock et al., 1994; Mock et al., 1997; Mock et al., 2005; Schwartz, 2000a; Schwartz, 2000b; Schwartz, Mori, Gao, Nail, & King, 2001), nausea (MacVicar & Winningham, 1986; MacVicar, Winningham, & Nickel, 1989; Mock et al., 1997), and weight change (MacVicar & Winningham, 1986; Schwartz, 1999; Schwartz, 2000b; Segal et al., 2001). It is well recognized that treatment for cancer may contribute to loss of exercise capacity and physical function, and that this effect may persist five years or more after treatment completion (Thompson, Gordon, & Pescatello, 2010). Aerobic exercise interventions during and after chemotherapy and/ or radiation treatment for breast cancer have also been beneficial to both physical functioning (Campbell et al., 2005; Mock et al., 1997; Mock et al., 2001; Mock et al., 2005; Mutrie et al., 2007; Pinto, Frierson, Rabin, Trunzo, & Marcus, 2005; Schwartz, 1999; Schwartz, 2000a; Schwartz, 2000b; Segal et al., 2001), and exercise capacity (Courneya et al., 2007; Crowley, 2003; Drouin, 2002; Kim, Kang, Smith, & Landers, 2006; MacVicar & Winningham, 1986; MacVicar et al., 1989; Schwartz, 2000b). Additionally, improvements in lean body mass (Battaglini, 2004; Drouin, 2002; Winningham, MacVicar, Bondoc, Anderson, & Minton, 1989), bone

mineral density (Schwartz, Winters-Stone, & Gallucci, 2007), and quality of life (Campbell et al., 2005; Daley et al., 2007) have been reported. In breast cancer survivors, there is a significant negative association between physical activity and all-cause mortality (Sternfeld et al., 2009). In addition, regular exercise is known to be effective in the prevention and control of many comorbidities that are commonly reported both before and after diagnosis of breast cancer, such as cardiovascular disease, diabetes, hypertension and obesity (Eley et al., 1994; Fletcher et al., 1996; Yancik et al., 2001). Overall, it is well established that there are many positive benefits resulting from exercise during and after chemotherapy and radiation treatment for breast cancer.

Breast cancer treatment

A clear understanding of the treatment for breast cancer and its effects on the physiological response to exercise is required to develop optimal guidance for exercise in patients and survivors. Women treated for breast cancer may receive both local and systemic therapies, depending on their specific diagnoses.

Local therapies, which target the affected area of the body, include surgery and radiation. Surgery is performed to remove the tumour or check for the spread of cancer. Radiation involves a high-energy beam targeted to the affected area, to damage the DNA of the cells within the path of the beam.

Systemic therapies, which affect the whole body and are not localized to the site of the tumour, include chemotherapy and hormonal therapy. Chemotherapy is a cytotoxic treatment; it targets and kills rapidly dividing cells in the body. While this mode of treatment is effective at killing cancer cells, chemotherapy also affects other rapidly

dividing cells such as bone marrow, gastrointestinal mucosa, gonads and hair follicles, and may have an affinity for certain organs, causing damage or organ toxicity (Wilkes, 1996). Hormonal therapy is used to block estrogen and progesterone, which can promote the growth of breast cancer cells. There are two common types of hormonal therapy used to treat breast cancer. The first is a selective estrogen receptor modulator (SERM), an anti-estrogen; it blocks estrogen from attaching to estrogen receptors on breast cells. The most common type of SERM used in breast cancer treatment is Tamoxifen. Aromatase inhibitors are the second type of hormonal therapy, which work by blocking an enzyme that helps produce estrogen within the body.

Targeted therapy is another type of treatment that is used in treatment of the approximate 25% of breast cancers that exhibit amplification of the HER-2 gene, which causes uncontrollable cell reproduction. Trastuzumab is a monoclonal antibody developed for treating this sector of the population (Browne, O'Brien, Duffy, Crown, & O'Donovan, 2009). Trastuzumab selectively binds to the HER-2 proteins to prevent reproduction. However, HER-2 proteins can develop resistance to Trastuzumab, so other HER-2 antagonists are in development (Browne et al., 2009).

It is not uncommon for women with breast cancer to receive both local and systemic treatments outlined above, while targeted therapy is only used in those diagnosed with a breast cancer that overexpresses HER-2. Hormonal therapy typically occurs after initial treatment with surgery, chemotherapy and radiation, while targeted therapy can occur during chemotherapy or following initial treatment.

Side effects

There are a number of side effects of breast cancer treatment that have the potential to affect the body's response to exercise.

Side effects of surgery are usually localized to the incision site and can include pain, swelling and tenderness. Decreased range of motion and lymphedema are also possible side effects of surgery. Although surgery and its side effects may lead to a temporary period of inactivity, it is unlikely to affect the exercise response (Jones, Eves, Haykowsky, Freedland, & Mackey, 2009).

SERMs can cause serious side effects including blood clots, stroke and endometrial cancer. Other symptoms can include chest pain, shortness of breath, weakness, dizziness, fatigue, hot flashes, headache and mood swings. The most common initial side effect of aromatase inhibitors is joint pain or stiffness. Long-term side effects of aromatase inhibitors are not clear, but appear to include an increase in osteoporosis and/or fractures (Winer et al., 2005). There is potential for hormonal therapies to affect the exercise response, but this relationship remains largely speculative (Jones et al., 2009).

Side effects of radiation are limited to the treated area, but radiation therapy for breast cancer can involve the heart and lungs in the beam path. Fatigue, myelosuppression, cardiotoxicity and pulmonary toxicity are reported side effects of radiation, as well as lymphedema and skin irritation (Shapiro & Recht, 2001).

As chemotherapy is administered systemically, side effects can occur throughout the body. Side effects occurring during the course of chemotherapy treatment are referred to as short-term, or acute side effects and will usually resolve within months of treatment completion (Partridge, Burstein, & Winer, 2001). Long-term or chronic effects

have later onset, typically after the course of treatment and may last for many years (Canadian Cancer Society/National Cancer Institute of Canada, 2008). Chronic effects may also result due to an accumulation of damage that begins during treatment. Some of the most common acute side effects are fatigue, nausea, vomiting, diarrhea, hair loss, weight gain, sores and dryness in mouth, myelosuppression (Partridge et al., 2001), cardiotoxicity and pulmonary toxicity (Hsieh et al., 2008). Cardiotoxicity and pulmonary toxicity, as well as several other organ toxicities can occur as long-term side effects as well.

Trastuzumab is also associated with cardiotoxic side effects, and is often used in combination with chemotherapy and thus may contribute to the cardiotoxicity experienced during this period.

Of the side effects described above, those resulting from chemotherapy and radiation have the strongest potential to alter the affected individual's response to exercise. As such, from this point on, the literature review will focus on chemotherapy and radiation treatments.

A further factor that requires consideration in the effect of breast cancer treatment on the exercise response is the timing of treatment. For example, there is a distinction between individuals who are currently undergoing initial treatment (especially chemotherapy and radiation) for breast cancer (patients), and those who have finished initial treatment (survivors). While survivors are finished surgery, chemotherapy and radiation treatment, they may receive hormonal therapy or targeted therapy for 5 or more years following initial treatment. Survivors may still be recovering from acute side effects from previous treatment, and/or experiencing chronic or cumulative side effects. However, the side effects of chemotherapy and radiation treatment tend to peak during

treatment, as such patients are likely to be experiencing a greater number of, and more severe variants of side effects.

Breast cancer treatment and exercise

Several of the aforementioned side effects of chemotherapy and radiation affect the hematopoietic, pulmonary and cardiovascular systems. All of these systems are integral to generating the physiological response required to meet the increased demand for oxygen during exercise. There are three side effects in particular, that have a high potential to alter exercise physiology in a breast cancer patient or survivor. These side effects, decreased red blood cell (RBC) production, cardiotoxicity and pulmonary toxicity, will be the focus of discussion due to their combined high prevalence and dramatic effect on the response to exercise.

Myelosuppression is a side effect of both chemotherapy and radiation where the bone marrow's ability to replace used blood cell elements, such as RBCs is decreased (Wilkes, 1996). Decreased RBC production can lead to anemia, which occurs in 30-90% of patients with cancer (Knight, Wade, & Balducci, 2004). Although there are interventions available, such as transfusion and erythropoietin stimulators, the treatment of anemia does not seem to be a priority, as very few breast cancer patients actually receive these treatments during adjuvant chemotherapy (Goldrick et al., 2007). During exercise in otherwise healthy people, anemia is associated with a reduction of maximal oxygen consumption (VO_{2max}), an indication of aerobic fitness, and both maximal (Zarychanski & Houston, 2008) and submaximal performance (Sorace & Patzan, 2007). The reduced oxygen content of the blood with anemia causes cardiac output and muscle blood flow to increase at a greater rate during exercise, and remain higher

relative to the intensity of exercise through the workout (Sorace & Patzan, 2007). Due to these alterations in cardiac output, heart rate will increase quicker and remain higher throughout exercise.

Chemotherapy, radiation and Trastuzumab have all been associated with cardiotoxicity. Certain chemotherapy drugs used to treat breast cancer can cause permanent or transient adverse effects to the myocardium. The mechanism of cardiomyocyte damage is thought to be free radical generation by the drug leading to oxidative stress (Bird & Swain, 2008). Intracellular calcium influx and overload are also linked with cardiomyocyte membrane damage and cell death, respectively (Shan, Lincoff, & Young, 1996). Radiation-induced cardiotoxicity has the potential to affect all structural components of the heart, rather than just the myocardium, as is common with chemotherapy (Berry & Jorden, 2005). The specific mechanism of Trastuzumab-induced cardiotoxicity is not clearly defined, but there is an increased incidence when used in combination with chemotherapy (Perik et al., 2007).

Cardiotoxicity may present as a variety of clinical manifestations. Some examples include tachycardia, bradycardia, other arrhythmias, decreased left ventricular ejection fraction (LVEF), diastolic dysfunction, pericarditis, myocarditis, cardiomyopathy, myocardial ischemia, myocardial infarction, and heart failure (Bird & Swain, 2008; Dempsey, 2008; Floyd et al., 2005). Many of the effects of cardiotoxicity are asymptomatic or silent, which often leaves structural changes that may affect cardiac function and performance during exercise undetected. The predominant indicator of cardiotoxicity is decreased contractility of the left ventricle (Ewer & Lenihan, 2008). The criterion used to indicate cancer treatment-induced decreased cardiac contractility is a decreased LVEF, however this measurement is known to lack

sensitivity in detecting cardiomyocyte damage (Ewer & Lenihan, 2008). Chemotherapy drugs used to treat breast cancer are some of the most cardiotoxic drugs (Dempsey, 2008); yet, the actual prevalence is likely greatly underestimated by this insensitive measurement technique (Ewer & Lenihan, 2008). Most reported prevalence rates cite only severe cases of cardiotoxicity (i.e. heart failure), while the extent of damage that is required to affect the cardiac response to exercise is considerably less. Modern radiation techniques limit the exposure of the heart to radiation, and follow-up with patients who have received this treatment have not shown an increased risk of cardiac disease (Shapiro & Recht, 2001). However, there is a trend toward higher incidence of cardiac perfusion defects (an indication of heart disease) with increasing volume of left ventricle exposed to radiation (Marks et al., 2005). Overall, reported prevalence rates of cardiotoxicity do not effectively represent the extent to which breast cancer treatment affects the heart.

Some of the manifestations of cardiotoxicity discussed would be contraindications to exercise, but for the less severe conditions, and for any myocardial damage preceding onset of the more severe conditions, there are alterations to the cardiac response to exercise that can be predicted. For example, damage to the myocardium would result in decreased myocardial contractility, in which case preload is much less effective in increasing stroke volume; and with arrhythmias, such as bradycardia or tachycardia the relationship between heart rate and oxygen consumption would be altered.

Pulmonary toxicity can occur through direct or indirect (via a signal transduction pathway) damage leading to cell apoptosis and a loss of integrity in pulmonary capillaries, resulting in a loss of lung compliance, decreased gas exchange, and even

respiratory failure (Abid, Malhotra, & Perry, 2001). Pulmonary toxicity is much easier to detect than cardiotoxicity. An insidious onset of dyspnea associated with a nonproductive cough is the typical symptom associated with chemotherapy-induced pulmonary toxicity, and can aid in early diagnosis (Abid et al., 2001). There is also a test for pulmonary toxicity that has enough sensitivity to detect abnormalities prior to symptoms (Camp-Sorrell, 2005). The literature shows that pulmonary toxicity is more common in chemotherapy drugs used to treat non-breast cancers, with documented incidence rates of up to 40% (Abid et al., 2001). Prevalence has not been assessed for most of the current adjuvant chemotherapy protocols commonly used for breast cancer (Yerushalmi et al., 2009). However, one recent study that specifically investigated pulmonary function following breast cancer chemotherapy, showed a decline in carbon monoxide diffusion capacity, adjusted for hemoglobin levels, in all 34 subjects, while only five reported dyspnea (Yerushalmi et al., 2009). This study suggests that like cardiotoxicity, the prevalence of pulmonary toxicity in breast cancer treatment may be underestimated. Pneumonitis is the clinical syndrome associated with radiation-induced pulmonary toxicity. It is fairly rare, occurring in less than 1% of women treated with radiation alone, with a higher incidence when chemotherapy is given concurrently (Shapiro & Recht, 2001).

Chemotherapy-induced damage to the lungs may ultimately result in restrictive lung disease, decreased lung volume, increased work of breathing and impaired gas exchange (Camp-Sorrell, 2005). Hypoxemia will occur as a result of impaired oxygen diffusion coupled with uninterrupted perfusion to damaged areas of the lung (Camp-Sorrell, 2005). This low oxygen concentration in the blood results in impaired oxygen delivery to the muscles, especially during exercise.

In summary, chemotherapy and radiation treatment for breast cancer can result in several mechanisms of damage resulting in side effects that alter the hematopoietic, cardiovascular and pulmonary systems. With the knowledge of anemia's effects in otherwise healthy individuals, the effect of myocardial damage on heart contractility and the effect of impaired gas exchange at the alveoli, an approximation of the repercussions of chemotherapy and radiation treatment on the cardiovascular exercise response can be inferred. Specifically, these side effects cause a change in stroke volume due to decreased myocardial contractility, and impaired oxygen delivery due to impaired oxygen carrying capacity of the blood and impaired gas exchange. At rest and light activity, the cardiovascular system can typically compensate for these impairments in oxygen delivery to tissues through an increase in heart rate to compensate for the decreased stroke volume. However, when exercise is performed, the ability to compensate is not enough to fulfill oxygen requirements of metabolically active muscles. During exercise in a healthy individual, blood flow is shunted from the less active tissues, via vasoconstriction in viscera arterioles, toward the respiratory muscles and skeletal muscles being used, via vasodilation in skeletal muscle arterioles, enhancing oxygen delivery to these tissues. As the exercise intensity increases, the amount of oxygen consumed and delivered to the exercising muscles increases concurrently (Cardiovascular dynamics during exercise, 2005). The increased demand for oxygen is met by increased responses in cardiac output and pulmonary oxygen diffusion capacity. Individuals treated for breast cancer may experience decreased responses in these parameters, and the decreased oxygen carrying capacity of the blood, as experienced by most cancer patients, will compound this effect. For these individuals, an altered response to exercise would occur: oxygen delivery is not

effectively increased to meet the increased requirement, thereby negatively affecting exercise capacity.

With an approximation of the specific cardiovascular ramifications of chemotherapy and radiation treatment side effects, the effect on exercise prescription can be inferred. The Fick equation states that maximal oxygen consumption is equal to the product of cardiac output and arteriovenous oxygen content difference. There are three determinants of oxygen consumption by tissue. The first determinant is the rate at which oxygen is transported to the tissues, by way of blood flow. Blood flow increases very quickly in response to an increase in heart rate. In addition to alterations in the vascular system to redirect blood flow during exercise, an increase in blood flow is mediated by an increase in cardiac output. Cardiotoxicity is likely to result in diminished stroke volume combined with reduced ability to increase stroke volume in response to exercise, which would limit the increase in cardiac output and thereby blood flow in affected individuals during exercise. The second determinant is the oxygen-carrying capacity of the blood. Anemia occurs in up to 90% of cancer patients to varying degrees, and is a reduction in oxygen-carrying capacity of the blood. The last determinant of oxygen consumption is the amount of oxygen extracted from the blood. Although the arteriovenous oxygen content difference, a measurement of this determinant, can be affected in cancerous cells when compared to normal tissue, it is unknown whether any change occurs in a cancer patient's skeletal muscle (Beaney, Jones, Lammertsma, Mckenzie, & Halnan, 1984). Maximal oxygen consumption is likely to be negatively affected by these alterations of the determinants of oxygen consumption in breast cancer patients. The individual's heart rate response to exercise is also affected. Specifically, heart rate is higher for any given submaximal exercise

intensity or workload due to the need for compensation for lower cardiac output. Metabolism is also likely to be affected, as the cardiovascular system has to work harder for any given workload to maintain oxygen delivery, which would increase energy expenditure.

Evidence of these inferred alterations in the response to exercise are confirmed by a recent study. This cross-sectional study compared cardiovascular parameters of women who were treated for breast cancer with surgery, chemotherapy, radiation and hormonal therapy, to those of age-matched healthy, control subjects (Jones et al., 2007). Both absolute VO_{2peak} (a term used to represent VO_{2max} in clinical populations) and VO_{2peak} relative to body weight were lower in the breast cancer survivors. Resting cardiovascular function differed significantly by heart rate, systolic blood pressure, both of which were higher in the breast cancer survivors, and stroke volume, which was lower. Cardiac output and the arteriovenous oxygen content difference were similar in both groups at rest. Comparison of these parameters indicate that at rest, the cancer survivors experienced an increased heart rate to compensate for their lower stroke volume in order to maintain cardiac output. At peak cardiovascular function, the cancer survivors' stroke volume was still significantly lower and cardiac output was also significantly lower, yet maximal heart rate did not differ. Again, no difference in arteriovenous oxygen content difference was observed. There was no difference in systemic vascular resistance, a measure of afterload, between groups at rest or peak function. The lack of difference in peripheral contributions to maximal oxygen consumption (arteriovenous oxygen content difference) indicates that the source of the significantly lower VO_{2peak} in the breast cancer survivors can be attributed to central limitations (the lower maximal cardiac output and stroke volume). Similarly, the lack of

difference between two determinants of stroke volume (afterload and maximal heart rate) indicates that the lower maximal stroke volume of the breast cancer survivors can be attributed to the other remaining determinants of stroke volume (ventricular preload and/ or contractility) (Jones et al., 2007).

Although no values were reported for submaximal exercise, comparison of the amount of change from resting to peak cardiovascular function between the cancer survivors and the healthy controls gives an indication of the alterations associated with the cardiovascular response to exercise due to breast cancer treatment. At rest, the cancer patients had a higher heart rate than controls, yet the maximal heart rates were similar, meaning that heart rate reserve was much smaller in the cancer patients (increases of 68% vs. 103%). Even though stroke volume was significantly lower at both rest and peak in the cancer patients, the increase from rest to peak was similar between the two groups (10%). This implies that the effect of the decreased contractility of the heart in cancer patients that leads to the decreased stroke volume at rest was not magnified by exercise. Cardiac output was similar at rest, but increased much more in the control group (125% vs. 86%), which was a function of this group's greater heart rate reserve. Although, limited by the cross-sectional design, this study provides an important glimpse into the cardiovascular sequelae of breast cancer treatment as they affect the response to exercise. Interpretation of these results with respect to their applicability to breast cancer patients currently receiving chemotherapy or radiation treatment must be cautioned as the assessment of cardiovascular function was performed on average three years following completion of chemotherapy. However, it could be hypothesized that these differences would only be magnified during treatment, as this is when the side effects tend to peak (Courneya & Mackey, 2001).

Exercise prescription

Although there is an abundance of research results in the literature that indicate the positive benefits of exercise on several outcomes in the breast cancer population, there are additional studies with inconclusive results, even for the same outcomes. A possible explanation for this lack of consensus is that the effect of exercise in cancer research may be underestimated by the use of imprecise measurements of physical activity and exercise (Ballard-Barbash et al., 2002). The limited control over the amount and intensity of exercise in many of the studies conducted thus far complicates the interpretation and comparison of results among studies (Knutsen, Quist, Midtgaard, Rorth, & Adamsen, 2006). However, exercise interventions have recently become more structured and use more objective physiological techniques to describe the effects of aerobic exercise (Knutsen et al., 2006). Although the description of exercise has improved, typically studies have only compared a single exercise prescription to a control group, and have not evaluated the merits of one prescription over another (Courneya & Mackey, 2001).

The dearth of comparative studies and the inability to compare results between different studies renders the available literature insufficient to make evidence-based recommendations for exercise prescription. Guidelines on exercise for cancer survivors were published recently as a result of a roundtable consensus convened by the American College of Sports Medicine (ACSM) (Schmitz et al., 2010). One outcome of the consensus was that overall, there is overwhelming evidence that exercise is safe and effective in achieving several beneficial outcomes both during and after treatment for breast cancer. However, for specific guidelines for exercise prescription, reference to

the general population age-appropriate physical activity guidelines for Americans is recommended, with brief precautions listed for specific cancer types. It is noted however, that prescription should be individualized according to a number of patient-specific factors including physiological changes due to negative treatment side effects, and that this type of prescription is lacking in the current literature.

Future studies are needed to fill crucial gaps in the literature. In order to optimize outcomes, the aerobic exercise prescription must have a firm scientific basis. To establish a scientific basis sufficient to determine optimal exercise prescription guidelines, future studies should adhere to two important stipulations regarding exercise prescription. First, increased regulation of the exercise prescription employed is necessary, including improved control over the components of the exercise prescription, and further refinement of the use of physiological descriptions of the exercise prescription. Second, the prescription should be individualized to accommodate inter and intra-individual factors specific to the population, such as physiological changes as a result of treatment. Adherence to these guidelines should improve the quality and consistency of exercise intervention studies and improve the ability to compare resulting outcomes.

Aerobic exercise intensity

In the general population, aerobic exercise capacity, or fitness (VO_{2max}), is associated with a decreased risk of cardiovascular disease that is more than twice as large as the decreased risk associated with general physical activity (Swain, 2005), and is the strongest prognostic marker established (Keteyian et al., 2008). This relationship is especially important for breast cancer survivors who are speculated to be at a greater

risk for cardiovascular disease than the general population (Jones, Haykowsky, Swartz, Douglas & Mackey, 2007). What is more, a dose-response relationship is seen between VO_{2max} and reduced risk of all-cause mortality (Blair et al., 1995). A dose-response relationship is also seen with the volume of exercise, which encompasses frequency, intensity and duration of exercise, and fitness improvements (Thompson et al., 2010). Taken together, these findings emphasize that exercise that results in improvements in VO_{2max} should be a priority.

There are four components that describe exercise and should be included in an exercise prescription: frequency, intensity, time or duration and type (Thompson et al., 2010). Perhaps the most contentious, yet most important of these components is the intensity of aerobic exercise. Exercise intensity is measured or expressed as the percentage of an individual's VO_2 reserve (VO_2R), which is the difference between VO_{2max} and resting oxygen consumption (VO_{2rest}). Other values used to express intensity include the percentage of VO_{2max}, which may be the most common, or peak oxygen consumption (VO_{2peak}), which is often used in non-athletic populations. Exercise intensity may be considered the most influential parameter in improving VO_{2max} (Davis & Convertino, 1975; Swain, 2005). However, determination of the appropriate level of intensity in an exercise prescription for both healthy and diseased populations requires several important considerations.

In the general population, there exists a minimum intensity threshold above which health and fitness benefits will occur (Thompson et al., 2010). The threshold intensity is influenced by initial fitness. In an extensive review of exercise intensity studies, subjects with initial VO_{2max} values below 40 mL O_2/kg/min exhibited significant increases in VO_{2max} even with exercise intensity levels as low as 28-32% of VO_2R

(Swain & Franklin, 2002). In contrast, those whose initial VO_{2max} values were above 40 mL O_2/kg/min only experienced increases in VO_{2max} at exercise intensities above 46% VO_2R. Although exercise at the minimum intensity threshold will improve VO_{2max}, intensities above this threshold, and high intensity aerobic intervals, are more effective at increasing VO_{2max}, and decreasing the risk of coronary heart disease (Swain, 2005; Swain & Franklin, 2006). For example, nine studies that held the total energy expenditure of exercise constant, but varied the intensity across groups showed greater increases in VO_{2max} with exercise at a vigorous, versus a moderate or lower intensity (Swain & Franklin, 2002). Although some benefits occur from exercise at a low intensity for those with a VO_{2max} under 40 mL O_2/kg/min, greater benefits occur with higher intensity exercise. This specific relationship has yet to be confirmed in clinical populations.

Another area of research that indicates the importance of exercise at a higher intensity is interval training. Aerobic interval training involves the alternation of a specified bout of time at a relatively high intensity, and a specified bout of time at a lower intensity to allow for recovery. This type of exercise training induces larger beneficial effects on fitness and cardiac parameters than continuous training at a moderate or low intensity. Findings include larger improvements in VO_{2max} and stroke volume in human male subjects, and improved cardiac contractility capacity of cardiomyocytes in rats with heart failure (Wisloff et al., 2007). The potential of interval training to improve contractility in damaged areas of the myocardium may be particularly useful to the breast cancer population who has received cardiotoxic chemotherapy regimens. One study in particular showed improvements in VO_{2max} and cardiac parameters in rats that were twice as large in the group that performed high

intensity interval training compared to the group that performed only moderate intensity interval training (Kemi et al., 2005). In another, high intensity exercise training restored the function of damaged cardiomyocytes to levels comparable to sedentary, healthy control rats (Wisløff, Loennechen, Currie, Smith, & Ellingsen, 2002). The extent of the improvement in cardiomyocyte function seen in rats with high intensity exercise creates a strong case for the investigation of similar training protocols in humans, with particular relevance for the breast cancer population.

Although high intensity exercise may be more beneficial than lower intensities, a maximum intensity threshold may exist, especially for clinical populations, above which potential health risks may be introduced. Exercise increases demand on the cardiovascular, pulmonary and skeletal muscle systems, which creates the potential to exacerbate any dysfunction of these systems that may exist in unhealthy or diseased individuals. This maximum intensity threshold is less clearly delineated in the literature than the minimal threshold, yet the concept of its existence is recognized. For example, it is recommended that the intensity of exercise be taken into account with exercise interventions in cancer patients, so that the benefits can be maximized safely (Winningham, 2000). A specific health concern with regards to exercise intensity for cancer patients is the immune system. In studies on the general population, exercise volume has been shown to influence the immune system, where a moderate dose has a positive effect and intense exercise or no exercise may have a negative effect (Schneider, Dennehy, & Carter, 2003), however, the effect of aerobic exercise training on the immune system of breast cancer patients is inconclusive (Drouin, 2002). Other concerns for cancer patients with regard to high exercise intensity include those associated with side effects such as cardiotoxicity, pulmonary toxicity and anemia.

Symptoms of these side effects such as fatigue may prevent affected individuals from achieving a high intensity and may therefore affect exercise adherence, according to self-efficacy theory, if individuals are consistently unable to achieve their exercise prescription (Woodgate, Brawley, & Weston, 2005). The other concern with these side effects is the possibility of exacerbation due to high demand on the cardiovascular system. These concerns indicate that the risk-to-benefit ratio of high intensity exercise in breast cancer patients may be higher than that of the general population (Courneya, Mackey, & McKenzie, 2002). The concept of a maximum threshold is an important feature of an aerobic exercise prescription and should represent an intensity that is both safe and feasible. With these two thresholds in mind, the optimal exercise intensity for cancer patients represents a balance between improving VO_{2max} to achieve health benefits and avoiding negative health consequences.

As the specific level of aerobic exercise intensity is important to achieving optimal health and fitness benefits, the prescription of aerobic exercise intensity is a procedure that deserves appreciable attention. There is a variety of tools commonly used to guide exercise intensity prescription and quantify exercise intensity including physiological measurements like heart rate (HR) and oxygen consumption (VO_2), and subjective measurements like rating of perceived exertion (RPE). There are various methods of exercise intensity prescription that make use of these tools. According to the ACSM, there are no studies available comparing all exercise intensity prescription methods simultaneously and thus it not known how intensities achieved by each method compare to each other (Thompson et al., 2010). The ability to interpret and compare methods of exercise intensity prescription is necessary to make evidence-based recommendations on this particular parameter of exercise prescription. In

contrast, if reported fully and accurately, frequency, duration and mode of exercise can be compared between studies with much less ambiguity.

In addition to the inability to compare the intensity achieved by each method, there is a lack of knowledge regarding the accuracy of each method individually in the breast cancer population. As described above, the effects of breast cancer treatment are postulated to be significant moderators of the exercise response. The combination of cancer and treatment type, and the stage of treatment (patient vs. survivor) are all factors that could alter the tools used in exercise intensity prescription directly (such as HR, VO_2), or indirectly (such as RPE). Alterations in the relationship between these tools and exercise intensity would theoretically also cause changes in the physiological constants, relationships and assumptions that form the basis of the different methods of exercise intensity prescription. The presence of altered physiology in these populations introduces a potential for disparity in the accuracy, effectiveness and relationship of the different methods of exercise intensity prescription when compared to healthy individuals. The importance of exercise intensity for health outcomes indicates that knowledge of the actual intensity of exercising breast cancer patients and survivors is essential, and intensity prescription methods that do not accurately elicit the intended intensity are not ideal in this population.

In summary, the exercise prescription is not well described nor controlled in many previous studies of cancer and exercise, possibly causing an underestimation of the effect of exercise and precluding the comparison of different studies. More objective physiological measurements are needed in future studies tasked with determining the optimal exercise prescription. Of the four components of exercise prescription, aerobic exercise intensity is the most important in influencing health and fitness benefits, and is

also the most difficult to compare among studies due to the lack of ability to compare the different techniques used. In addition, the potential for differences in the exercise response due to the presence of cancer and treatment type suggest that there may be differences in accuracy of the exercise intensity prescription methods in populations differing in these aspects.

Aerobic exercise intensity prescription methods

As suggested earlier, exercise intervention studies cannot be easily compared if they utilize different methods of exercise intensity prescription because it is unknown how they compare in terms of the intensity achieved. Aerobic exercise intensity is specified and described in an exercise prescription by way of a target. There are three main tools used to prescribe intensity of aerobic exercise including target heart rates (THR), target subjective ratings of exertion and target workloads (Swain, 2000). Combinations of these three tools can also be used. For some of these tools, like THRs, there are several different methods of prescribing intensity. Each method of intensity prescription generates targets corresponding to specific exercise intensities. The underlying assumption is that the achievement of the target will elicit a specified VO_2, usually expressed as a percentage of VO_{2peak} or VO_2R.

Target heart rate (THR)

One of the most common methods of prescribing exercise intensity is by providing a THR, typically in the form of a range of HRs. HR can be easily used to quantify exercise intensity as it provides an immediate and objective physiological index of effort. For aerobic exercise intensity prescription, a THR is given that is intended to

correspond to a specific exercise intensity. A THR can be determined by the direct HR method, HR reserve (HRR) method, or percentage of maximal heart rate method ($\%HR_{max}$). These three methods differ substantially in the technique by which a THR corresponding to the desired intensity ($\%VO_2R$) is determined.

The $\%HR_{max}$ method is the oldest and simplest method of the three (Whaley, Brubaker, & Otto, 2006). The THR is taken from a percentage of the maximal heart rate (HR_{max}) for each individual. The HR_{max} of each individual can be predicted using an equation based on age, or measured during a maximal incremental exercise test. In its simplest form, this method uses a prediction equation based on the age of the subject to determine HR_{max}. However, there is a high degree of variability in HR_{max} among individuals, and the traditional prediction equation, 220-age, often leads to an underestimation for ages less than 40 and overestimation for ages over 40 (Thompson et al., 2010). A maximal incremental exercise test can be done to measure HR_{max} with a cycle ergometer or a treadmill and a HR monitor. However, maximal exercise testing may not always be feasible or safe for all populations. A review of exercise testing in cancer studies indicates that maximal exercise testing is relatively safe in the cancer population (Jones, Eves, Haykowsky, Joy, & Douglas, 2008).

There are several other considerations necessary regarding the use of the $\%HR_{max}$ method. First, it is very inaccurate at low intensities, and may lead to prescription of a THR lower than the individual's resting heart rate (HR_{rest}). Second, using a percentage of HR_{max} does not take into consideration the HR_{rest} of the individual. The relative intensity among individuals could vary greatly without accounting for their HR_{rest} (Thompson et al., 2010). Lastly, the percentage of HR_{max} does not directly correspond to the percentage of VO_2R; this method underestimates $\%VO_2R$ by

approximately 15%, with variance in this estimate depending on age and the level of exercise intensity (Pollock et al., 1998). As such, the percentage of HR_{max} used must be adjusted upwards to obtain the desired $\%VO_2R$.

The ACSM published guidelines on recommended percentages of HR_{max} corresponding to a few specific levels of exercise intensity for exercise prescription purposes (Pollock et al., 1998). In non-cancer populations, there are statistically significant differences between the percentages of HR_{max} required to elicit specific intensities (both VO_{2max} and VO_2R) and those percentages of HR_{max} recommended by the ACSM to elicit those intensities (Lounana, Campion, Noakes, & Medelli, 2007), indicating that although guidelines are in place to use this method, the prescription is likely still inaccurate. An unpublished analysis of exercise test data from 30 women who were exercise tested following chemotherapy for breast cancer at The University of British Columbia showed that the $\%HR_{max}$ required to achieve 50, 60 and 80% of VO_{2peak} is significantly different from the ACSM's recommendations for $\%HR_{max}$.

Although the $\%HR_{max}$ method requires minimal equipment and only a simple calculation to prescribe a THR, it has significant potential sources of error that may lead to an inaccurate intensity, and great variability in intensities achieved among individuals. Prescription methods that do not accurately and precisely achieve the desired intensity are not conducive to investigation of the specific effect of exercise intensity on an outcome, or in clinical practice, where certain intensities may be dangerous or ineffective. Thus, the rudimentary nature of this method indicates that it is not an appropriate choice for use in studies.

The Karvonen method, also known as the heart rate reserve (HRR) method is considered to be an accurate method of prescribing aerobic exercise intensity using

THRs (Ehrman et al., 2010). Similar to the %HR_{max} method, HR_{max} is used in this method, in either the predicted or measured form. The major difference between the two methods is that the HRR method also takes the HR_{rest} of the individual into account. HR_{max} and HR_{rest} are the only two values required to use this method, which makes it a feasible method, requiring only a cycle ergometer or treadmill and a HR monitor, the same equipment required to use the %HR_{max} method. The calculation required to determine a THR with this method is also quite simple. HR_{rest} is first subtracted from HR_{max} to obtain the HRR. The desired percentage of the HRR is then added to HR_{rest} to obtain the THR.

$$THR = ([HR_{max} – HR_{rest}] * \text{fractional intensity}) + HR_{rest}$$

A one-to-one linear relationship is assumed between %HRR and %VO_2R. In other words, the exercise intensity is considered equal to the percentage of HRR used to determine the THR. For example, 60% of an individual's HRR added to their HR_{rest} would achieve a THR thought to achieve an exercise intensity of 60% of VO_2R. Prior to a pioneering study in 1997 (Swain & Leutholtz, 1997), it was assumed that the percentage of HRR was equivalent to percentage of VO_{2max}. Swain and Leutholtz reasoned that comparing the range of HRs from resting (a nonzero value) to maximum, to a range of VO_2 values starting at zero and going to maximum introduced considerable error (Swain & Leutholtz, 1997). If these ranges are expressed as percentages of their maxima, the size of the error would be inversely proportional to fitness, as VO_{2rest} represents a higher percentage of maximum (Swain & Leutholtz, 1997). Similar to HRR, VO_2R is the difference between VO_{2max} and VO_{2rest}. Swain and

Leutholtz showed that %HRR more closely approximates $\%VO_2R$ than $\%VO_{2max}$ (Swain & Leutholtz, 1997). Since then, it has been generally accepted that $\%VO_2R$ has a linear relationship with %HRR (Ehrman et al., 2010; Pollock et al., 1998). The ACSM adopted %HRR and $\%VO_2R$ as the primary means of establishing exercise intensity in their 1998 position stand on recommended exercise quality and quantity (Pollock et al., 1998). This relationship has also been validated on a treadmill (Swain, Leutholtz, King, Haas, & Branch, 1998). After the discovery of this relationship in healthy subjects, it was also found in other populations including heart disease patients (Brawner, Keteyian, & Ehrman, 2002), diabetics (Colberg, Swain, & Vinik, 2003), the obese (Byrne & Hills, 2002), and elite cyclists (Lounana et al., 2007). This relationship has not been investigated in cancer patients.

The HRR method seems to introduce less variability and a more accurate conversion to exercise intensity, yet requires the same equipment and a similar simple calculation as the $\%HR_{max}$ method of determining a THR. The inclusion of HR_{rest} into the calculation of THR is easy and remedies many of the inconsistencies that are encountered when it is not included. However, the extent to which the relationship between %HRR and %VO2R exists in the breast cancer population needs to be established.

The final common method of establishing a THR is referred to as the direct HR method. This method is aptly named, as the THR is attained directly from the relationship between HR and VO_2 values recorded during a maximal incremental exercise test with cardiopulmonary measurements. To use this method, HR and VO_2 values are gathered at equal time increments (usually 15 seconds) for the duration of the exercise test via gas analysis techniques with a metabolic cart. These HR and VO_2

values are plotted and a linear regression is calculated. Using $\%VO_2R$ as the intensity gauge, the HR corresponding to the VO_2 consumed at the desired $\%VO_2R$ is taken as the THR for the desired intensity. This VO_2 value, the target VO_2 (TVO_2) can be calculated by the following equation:

$$\text{Target } VO_2 = (VO_{2max} - VO_{2rest}) * \text{fractional intensity} + VO_{2rest}$$

The THR can either be visually determined from the plot or it can be determined from the linear regression equation for the relationship. The HR corresponding to any given VO_2 expressed a percentage of VO_{2max} can also be used as the THR for prescription, if using $\%VO_{2max}$ as the gauge for intensity. Because this method is based on the relationship between HR and VO_2 as determined for each individual, it is recommended for use in individuals who may not exhibit a one-to-one relationship between the variables, such as those with low fitness levels, those with cardiovascular or pulmonary disease, or those taking medications (i.e. β-blockers) that alter the HR response to exercise (Whaley et al., 2006).

There is reason to believe that not only is this method fairly accurate, but that it remains stable in its ability to prescribe the desired intensity over time. A large study of 653 healthy but sedentary men and women showed that once the relationship between HR and $\%VO_{2max}$ has been established, it does not change, in that a THR continues to achieve the same relative intensity ($\%VO_{2max}$), even after exercise training has occurred (Skinner et al., 2003). These results indicate that this method can be used over the course of a training program without adjustment of the exercise prescription. However, in a study of training during chemotherapy treatment for breast cancer, there was a

change in relative exercise intensity for a given THR, suggesting that the use of this method in breast cancer patients may be limited without frequent re-testing (Kirkham, Campbell, Jespersen, & McKenzie, 2009). This study compared the HR-VO_2 relationship at baseline (prior to chemotherapy for breast cancer) to that following an exercise intervention for the duration of chemotherapy (median duration = 18 weeks). Results showed that using the direct HR method of exercise intensity prescription based on data collected prior to chemotherapy would not be accurate in terms of intensity achieved by the prescribed heart rate by the end of chemotherapy. This study is a direct example of how breast cancer treatment can directly affect exercise prescription. For example, the THR that would be prescribed to achieve an intensity of 75% of VO_{2max} for each individual subject before chemotherapy would actually achieve relative intensities ranging from 52-100% of VO_{2peak}, depending on the individual, by the end of chemotherapy treatment. Although it is unknown at what point during chemotherapy the change in the relationship occurs, it can be reasoned that for some portion of the intervention, participants may not be exercising at the intended intensity or may not be able to achieve their prescribed THR.

The direct HR method requires a metabolic cart, which is expensive, not always readily available, and requires a skilled operator, but is the recommended method of prescription for those who exhibit an altered HR and/ or metabolic response to incremental exercise. The calculation of the THR also requires more effort including the use of a computer rather than an ordinary calculator, in comparison to the other two methods of determining a THR. However, when a high level of accuracy is required, this method is a reasonable choice. Although, the relationship between the THR and the relative %VO_2R seems to remain stable in the general population, the HR-VO_2

relationship appears to change during exercise training concurrent with chemotherapy treatment for breast cancer. Further research is required to investigate how the HR-VO_2 relationship is affected by other cancer treatments and by treatment completion.

In summary, there are three common methods of determining a THR. Each of these methods is characterized by differing requirements in terms of equipment and calculations. The HRR and direct HR methods are considered to be more accurate in terms of achieving the prescribed exercise intensity than the $\%HR_{max}$ method, but the former two methods have not been compared directly. There is evidence that the HR-VO_2 relationship on which the direct HR method is based on changes due to chemotherapy treatment for breast cancer (Kirkham et al., 2009). It could be hypothesized that because chemotherapy affects this relationship, the one-to-one %HRR-$\%VO_2R$ relationship assumed in the use of the HRR method could also be altered by chemotherapy treatment. If this is true, then this method may not be accurate in the breast cancer population. It is also unknown whether these alterations in either relationship would remain following treatment. These are areas that require further investigation. Lastly, an important consideration in using any of the HR methods for exercise prescription purposes is that several factors including the environment, emotion and medications can influence HR and its relationship with VO_2 (The role of RPE in graded exercise testing. 1996).

Subjective rating of exertion

The use of a subjective rating of exertion target for prescription of exercise intensity is gaining popularity. The perception of exertion is the subjective intensity of

effort, discomfort, strain and fatigue during exercise (Robertson & Noble, 1997). Borg pioneered the scientific inquiry into perception of exertion in the 1960s. One of the primary areas of this discipline is the development and validation of a system for measuring or rating this perception of exertion. The most widely used instrument to indicate subjective rating of exertion is Borg's rating of perceived exertion (RPE) scale (Chen, Fan, & Moe, 2002). Borg believes that perceived exertion is the foremost indicator of the degree of physical strain (Borg, 1982). The subjective evaluation of perceived effort during exercise is believed to rely on a local muscle factor and a central cardiopulmonary factor (Eckblom & Golobarg, 1971). Borg claims that his scale integrates signals from the peripheral working muscles and joints, central cardiovascular and respiratory systems and central nervous system (Borg, 1982). It is assumed that local factors (muscles and joints) are the source of the primary sensor signals. Input from central factors (circulation and respiration) begins 30 to 180 seconds after initiation of exercise, and acts as an amplifier to the local signals (Robertson, 1982).

Borg created two different scales for rating perceived exertion. Borg's 15-point RPE scale was constructed to increase linearly with exercise intensity similar to the linear increase in HR and VO_2 (Borg, 1982). The values on the scale range from 6 to 20, and are intended to correspond to heart rates of 60 to 200 beats/min. The odd number values on the scale are accompanied by simple and easily understandable verbal expressions that help describe the level of intensity. For example a RPE of 14 would correspond to a HR of 140 beats/min. Borg however, acknowledges that this translation cannot be taken too literally, as a certain HR can correspond to differing levels of intensity depending on factors such as age, type of exercise, environment,

anxiety and other factors (Borg, 1982). Borg also created a category-ratio scale ranging from 0-10 (CR-10). The 6-20 scale is more commonly used for tests of perceived exertion, while the CR-10 is more often used clinically to rate dyspnea and pain (Borg, 1998). The CR-10 scale is not as well suited for exercise prescription purposes as the 6-20 scale, as its range is too small and it does not exhibit the parallel relationship to physiological measures that the 6-20 scale does.

There is growing evidence that prescription of a target RPE taken from the direct relationship between exercise intensity (%VO_2R) and RPE as measured during a maximal exercise test can be an effective prescription method. Perception of exertion was shown to be a better predictor of VO_{2max} than HR in both males and females in two early studies (Noble, 1982). In one study, tachycardia was induced in young, healthy, male subjects by parasympathetic blockade, causing a significantly higher HR than in control subjects for a given submaximal VO_2 (Eckblom & Golobarg, 1971). There were no significant differences in RPE for any given submaximal VO_2, indicating that RPE is not always strongly related to HR, but is more strongly related to VO_2. This is an interesting finding when applied to exercise intensity prescription in breast cancer patients, who often experience tachycardia as a manifestation of chemotherapy-induced cardiotoxicity (Bird & Swain, 2008; Floyd et al., 2005). The findings of this particular study suggest that despite an increase in HR relative to VO_2, RPE would continue to serve as guide to exercise intensity in symptomatic individuals. One study examined the use of RPE in women with breast cancer. This study compared the RPE of exercise at 40, 60 and 70% of VO_{2max} among breast cancer survivors and healthy controls. Subjects walked at a treadmill speed and grade corresponding to each of the intensity levels in three separate trials. There were no differences in the RPEs reported by the

breast cancer survivors and the controls at each intensity (Evans, Battaglini, Groff, & Hackney, 2009). Because breast cancer survivors perceive exercise intensity similarly to healthy controls, it can be assumed that the RPE method of exercise intensity prescription would have the same level of accuracy in this population as it would in others.

RPE has long been used in cardiac rehabilitation programs to prescribe exercise intensity (Noble, 1982). The use of RPE as the sole means of regulating exercise intensity is attractive because it does not require the use of physiological monitoring equipment. The only instrument necessary to perform training based on a basic exercise prescription using this method is a paper copy of the scale. However, the best way to attain the target RPE (TRPE) values given in the exercise prescription involves a graded cardiopulmonary exercise test where RPE and VO_2 are recorded at the end of each minute or workload of the test. Then, RPE is plotted against VO_2, to determine the relationship between RPE and exercise intensity. An advantage of this particular method of RPE exercise prescription is that the exercise test provides an opportunity to learn the scale prior to its use in training (Kang, Chaloupka, Biren, Mastrangelo, & Hoffman, 2009). In this method, RPE is “estimated” by the subject during the graded exercise test, and then the subject is asked to “produce” this RPE again during training. However, it should be noted that the psychophysical process required to reproduce an intensity from memory is not the same as the process of estimating an ongoing intensity (Noble, 1982). Empirical evidence showing the ability to produce previously estimated intensities is lacking (Dunbar et al., 1992). There are however, a few studies using this method that produced results that signify validity for this approach for some intensities (Dunbar et al., 1992; Glass, Knowlton, & Becque, 1992). Both studies used young male

subjects and compared HR and VO_2 between the estimation (graded exercise test) and production trials. The only significant difference in these parameters between the two trials was at an intensity of 70% of VO_{2max} on the treadmill in one study (Dunbar et al., 1992). The other intensity levels tested were 50% of VO_{2max} and 75% HRR, both with no significant differences in HR or VO_2. These two studies provide conflicting evidence of the accuracy of this method at higher intensities (70% of VO_{2max} and 75% HRR) on the treadmill. Thus, the accuracy of this method in prescribing exercise intensity remains unclear.

In summary, Borg's RPE scale is the most common method for measuring subjective rating of exertion during exercise. The 6-20 scale is designed to increase linearly with exercise intensity similar to the linear increase seen in HR and VO_2, making it a logical choice for prescribing exercise intensity. In the presence of an abnormal HR response to exercise, RPE has been shown to remain a fairly accurate indicator of exercise intensity (Eckblom & Golobarg, 1971). This factor, and a recent study showing that RPE is estimated similarly in breast cancer survivors and healthy controls (Evans et al., 2009) indicate that this method could potentially be effective in exercise prescription for the breast cancer population. The most effective method of using RPE in exercise prescription is to determine the relationship between RPE and VO_2 for each individual during a graded cardiopulmonary exercise test. Once this relationship has been established, only a paper copy of the scale is required for execution of the exercise prescription, making it a very feasible method. However, it should be noted that at higher intensities, evidence regarding the accuracy of this method is inconclusive.

Target workload

The third method of prescribing aerobic exercise intensity is by prescription of a target workload that is thought to elicit the desired intensity. Methods using a target workload for exercise prescription involve the use of metabolic equivalents and either the Compendium of Physical Activities or the ACSM metabolic equations.

The metabolic equivalent (MET) is a simple expression of the energy cost of physical activities as a multiple of the resting metabolic rate (RMR) (Byrne, Hills, Hunter, Weinsier, & Schutz, 2005). A constant value of 3.5 mL of O_2/kg/min is considered to be equivalent to 1 MET, and when expressed in relation to energy is 1 Kcal/kg/hour. The energy requirements of exercise are calculated by measuring oxygen consumption. One liter of oxygen consumed is equivalent to approximately 5 kcal of energy, and this relationship can vary depending on the predominant fuel source (Whaley et al., 2006). The factorial system of METs assigns an intensity level expressed as a multiple of 3.5 mL O_2/kg/min to an activity (Byrne et al., 2005). The MET system has been extensively used to evaluate current and past physical activity levels in epidemiological research, and by clinicians, practitioners and researchers to prescribe physical activities and exercise intensity (Byrne et al., 2005).

The Compendium of Physical Activities is a list of over 500 different activities that are each assigned a MET value as a rough measure of the energy expenditure each activity is thought to require (Ainsworth et al., 2000). This tool can be used to choose a physical activity that corresponds to a desired MET level or TVO_2. This use for exercise prescription is limited as the actual intensity elicited by each activity can vary greatly due to individual differences in efficiency and subjective level of effort exerted during the activity. The best application, and the original intended use of the Compendium of

Physical Activities is to facilitate coding of physical activities obtained from instruments used to gather data on physical activity history in observational studies (Ainsworth et al., 2000).

The best method of prescribing a target workload involves the use of metabolic prediction equations. The desired exercise intensity is expressed as a workload (treadmill speed and grade, or cycle ergometer power) that is associated with a desired level of energy expenditure (Whaley et al., 2006). This method of intensity prescription is useful for individuals whose HR response to exercise may be abnormal or inconsistent. The ACSM's metabolic equations use some known physiological constants for the oxygen cost of walking, running and cycle ergometry (Whaley et al., 2006). The TVO_2 corresponding to the desired exercise intensity is used in the equations to determine the target workload. For example, the equation for walking uses the oxygen cost constants of 0.1 mL O_2 per kilogram of body mass used to walk a distance of one meter and 1.8 mL O_2 per kilogram of body mass per one meter of vertical ground (incline).

Target VO_2 (mL O_2/kg/min) = 0.1*S +1.8*S*G + VO_2rest (mL O_2/kg/min)
Where S = speed (m/min), G = fractional grade (decimal form).

To use this equation in exercise prescription, the VO_2 corresponding to the desired intensity (%VO_2R), and a self-selected speed are plugged into the equation. VO_{2rest} can be measured or a constant can be used. The equation is then solved for grade. Together, the self-selected speed and grade would be given to an individual planning to exercise on a treadmill.

Another important physiological constant used in the calculation of target workloads is VO_{2rest}. As mentioned earlier, 1 MET is considered equivalent to the RMR, which is also considered equivalent to VO_{2rest}. These units are all considered to be constant at a value of 3.5 mL O_2/kg/min. The scientific basis for assigning a constant value to VO_{2rest} is quite weak. It is thought that this value representing one MET was derived from the VO_{2rest} of a single 70-kg, 40-year old man (Byrne et al., 2005). In one study that took particular precaution with procedures before and during measurement, 12 women and 12 men with an average age of 39 years had an average VO_{2rest} of 2.8±0.3 mL O_2/kg/min (Gunn et al., 2002). When this value of VO_{2rest} was used to calculate MET levels of different household activities, there was a significant difference from the MET level determined using the conventional 3.5 mL O_2/kg/min. This also changed the categorization of most of those activities from moderate (3-6 METs) to light (<3.0 METs), demonstrating the limitations of using an assumed constant that precludes an allowance for physiological variability among subjects (Gunn et al., 2002). Per kilogram, fat-free mass has a RMR 6.5 times as great as adipose tissue per day (Gunn et al., 2002). Based on these large metabolic rate differences, individuals with a higher percentage of body fat would be expected to have a lower RMR, and the physical activity intensity level, as in the previous study, would be underestimated by using the conventional MET value. In another study with a wide range of body mass indexes, the average VO_{2rest} for 763 subjects was 2.6 mL O_2/kg/min (Blair et al., 1995).

Variations in RMR suggest that the other physiological constants in the metabolic equations are also subject to variation. The correlation coefficient between measured VO_2 and workload typically ranges from 0.6 to 0.9 (Myers, 2005). This relationship is most often studied by comparing the relationship between the estimation of maximal

exercise capacity (VO_{2max}) by final treadmill workload on a graded exercise test (using the ACSM metabolic equation for walking), expressed in METs (eMET), versus the measured maximal MET value (mMET) (relative VO_{2max} divided by 3.5 mL O_2/kg/min). In cardiac patients, the eMET tended to overestimate the mMET (Myers, 2005). This inaccuracy has also been shown in other populations including healthy controls, individuals with at least one cardiovascular risk factor, and individuals with coronary artery disease, left ventricular dysfunction and heart failure (Maeder et al., 2008). Although this evidence only applies to the use of the metabolic equations in predicting VO_{2max}, it is likely that a similar relationship would be found with submaximal workloads as well. Based on the evidence that the metabolic equation tends to overestimate the VO_2 for a given workload, the prescribed workload would then be underestimated for a desired TVO_2.

In addition to the evidence of divergence from these “constants” in healthy populations, there is some evidence that breast cancer patients may experience intra-individual variance in metabolism as well. In two different studies, RMR significantly decreased from a measurement point prior to adjuvant chemotherapy treatment for breast cancer, to the midpoint of treatment, and then approached baseline values again at the end of treatment (Demark-Wahnefried et al., 1997; Harvie, Campbell, Baildam, & Howell, 2004). Similar to this finding, two studies that measured RMR pre-chemotherapy and at the end of chemotherapy found no change (Foltz, 1985; Kutynec, McCargar, Barr, & Hislop, 1999), and a third found no change at these time points or over each of four cycles of chemotherapy (Campbell, Lane, Martin, Gelmon, & McKenzie, 2007). Another study compared breast cancer patients receiving chemotherapy, to patients receiving localized therapy only, from diagnosis to one year

later. At the one-year follow-up, those patients who had received chemotherapy had gained fat mass, increased body fat percentage, and lost lean body mass, implying a decrease in RMR, while those who had received localized treatment had values similar to baseline (Demark-Wahnefried et al., 2001). However, the indirect measurement used to quantify RMR did not confirm any differences in these groups. A final study reported a decrease in RMR with the initial chemotherapy treatment, followed by an increase concurrent to increases in fat mass (Del Rio et al., 2002).

The aforementioned studies imply that there are inaccuracies in applying physiological constants to a healthy population and, in addition, metabolism may change temporally in patients during chemotherapy, and perhaps for an extended period of time for survivors following chemotherapy treatment. These findings question the accuracy of employing physiological constants as used in the ACSM's metabolic equations for prescription of exercise intensity. However, there is an important characteristic about this method that makes it attractive for use in any population, including cancer. This is the only method of exercise intensity prescription discussed that does not require the individual to moderate their effort (on a treadmill, this would be the speed and grade, on an exercise bike, the resistance). It is a very simple, cost effective and foolproof method that does not require use of a HR monitor or knowledge of a RPE scale. The exercising individual is simply provided with a treadmill speed and grade at which to exercise. However, it should be cautioned that the TVO_2 would reflect a different relative intensity with changes over time in VO_{2peak}. Therefore frequent re-testing would be required as fitness changes. Investigation of the use of the target workload method for intensity prescription in clinical exercise interventions is warranted by its ease of use.

Past, present and future of exercise intensity prescription method use in cancer and exercise research

Past method use

Unfortunately, the method used to prescribe aerobic exercise intensity in studies implementing an exercise intervention in cancer populations is often not clearly or accurately described, or is omitted from the publication. However, a general idea of the use of methods employed thus far can be extracted from these publications. First, because the method of exercise testing employed will dictate which methods of intensity prescription are possible, a review of exercise testing methods in cancer research will be discussed. A recent systematic review reported the proportion of cancer studies employing maximal, submaximal and other protocols of exercise testing (Jones et al., 2008). Only 31% of the intervention studies that used some form of exercise testing employed a maximal exercise test protocol with expired gas analysis, and 24% employed a maximal protocol without expired gas analysis, allowing for HR data collection only. A further 16% employed a submaximal exercise test protocol with a prediction equation for HR_{max} and VO_{2max}, and the others used 12 and 6-minute walk tests for a general indication of physical functioning.

The RPE method of intensity prescription could be used without any exercise testing, but as discussed above, the best way to prescribe an RPE to achieve a specific intensity is to use the relationship between RPE and VO_2 taken from a maximal exercise test with expired gas analysis. The direct HR method and the MET equation both require a VO_{2max} value, which, although it is not ideal, can be predicted from a submaximal exercise test. The HRR method could potentially be used without exercise

testing, if an age-predicted HR_{max} equation was employed. However, it is always preferable to measure HR_{max} and VO_{2max} on a maximal exercise test, because there is a great deal of variability involved in prediction (Whaley et al., 2006). All four methods of aerobic exercise intensity prescription described above could have potentially been employed in only 31% of studies.

In studies involving breast cancer patients or survivors that had an aerobic exercise intervention and reported the use of an aerobic exercise intensity prescription method, the $\%HR_{max}$ method of prescription with a predicted HR_{max} is most common. The next most common prescription method is the HRR method, again using a predicted HR_{max}. There are rare instances of others that report use of other measurements corresponding to $\%VO_{2max}$ such as blood lactate and cycle ergometer power. RPE is more often reported as an adjunct to other methods, but has also been used as the sole method of prescription. The direct HR method was used in one large, multi-centre, randomized control trial (D. C. McKenzie, personal communication, October 1, 2008) (Courneya et al., 2007), and is currently being used in another large multi-centre trial. No studies actually explicitly detail the use of the ACSM's metabolic equations as a prescription method, but some studies make allusions to it with phrases like "a pace was prescribed" and "a target is given for walking speed in relation to intensity." METs are used in some studies as measurements of total weekly exercise and to quantify exercise history in correlational exercise studies.

Present method use: Recommendations and guidelines

Current recommendations and guidelines for exercise prescription in cancer patients and survivors are based on the general recommendations for healthy and/or

aging adults (Thompson et al., 2010). There are no definite differences in the exercise prescription or the method of intensity prescription for cancer patients going through treatment and cancer survivors. In terms of aerobic exercise intensity, recommendations have been made in the form of %HRR, $\%HR_{max}$ and TRPEs (Courneya, Mackey & McKenzie, 2002). One author notes that HRR is the best method if HR_{max} is estimated (Courneya & Mackey, 2001). Another notes that RPE is best used in cancer patients who are on medications that alter the heart rate response to exercise (such as β-blockers) (Schneider et al., 2003). Exercise testing to VO_{2max} is recommended in exercise intervention studies, as it provides the most accurate portrayal of health and fitness outcomes (Jones et al., 2008; Schneider et al., 2003).

Future method use

A sizeable, yet crucial endeavour for future cancer and exercise research is creating a critical mass of evidence to determine the optimal exercise prescription for different cancer type and treatment combinations (Ballard-Barbash et al., 2002; Courneya & Mackey, 2001). Research aiming to address this research gap is increasingly dependent on precise physiological measurements such as VO_{2peak} (Knutsen et al., 2006), and requires proper documentation of each component of exercise prescription, especially intensity. More advanced aerobic exercise intensity prescription methods than the rudimentary $\%HR_{max}$ method are indispensable to this advancement. Overall, increased scientific demand for the effects of exercise at a specific intensity within cancer populations will catalyze a gravitation toward more rigorous documentation and the use of more accurate methods of aerobic exercise intensity prescription.

Conclusion

Breast cancer is prevalent around the world. Its treatment, although increasingly effective in decreasing mortality, is associated with negative side effects and long-term sequelae. Exercise has been explored as a technique of managing side effects, increasing fitness and reducing the risk of comorbid conditions in breast cancer patients and survivors. However, this relationship between exercise and breast cancer treatment is not one-sided; as certain side effects of breast cancer treatment, including, most notably, anemia, cardiotoxicity and pulmonary toxicity have the potential to alter the exercise response of affected individuals. In the breast cancer population, these side effects are prevalent and exhibit potential to significantly influence this response. Considering the idiosyncratic nature of the cardiovascular changes caused by breast cancer and its treatment, it seems clear that the optimal exercise prescription would have a firm scientific basis to address the specific needs of this population. It is well established that exercise is an effective therapeutic intervention in breast cancer patients and survivors, yet the evidence required to make population-specific recommendations for exercise prescription is lacking. Specifically, there is a lack of documentation of the effects of one exercise prescription versus another. This precludes the establishment of evidence-based guidelines for breast cancer patients receiving various treatments and breast cancer survivors following primary treatment. Extensive future research is required to achieve this goal.

Aerobic exercise intensity is an important parameter of exercise prescription and has documented positive associations with decreased mortality. There exists a minimal threshold intensity, above which health and fitness benefits will accrue and more

benefits are seen with a higher intensity. However, there is concern with high intensity exercise by cancer patients, as it may compromise the immune system or exacerbate side effects. Therefore, knowledge of the actual intensity of exercising breast cancer patients is essential and prescription methods that do not accurately elicit the intended intensity are not ideal in this population. The methods of aerobic exercise intensity prescription discussed in this review have been used, are recommended for use, and are likely to be used in future research of breast cancer and exercise interventions.

Objectives and hypotheses

This study will be a comparison of four common methods of exercise intensity prescription including the direct HR, HRR, MET equation and RPE methods, among breast cancer patients recently completing chemotherapy, breast cancer survivors who have completed initial treatment 1-3 years ago, and healthy controls. The results of this study will provide an index of the accuracy of each method in achieving an intended exercise intensity of 60% of VO_2R in breast cancer patients (objective 1), and breast cancer survivors (objective 2). This will allow comparison and interpretation of studies employing these different methods. The study will also determine whether being part of any of the three groups has an effect on the accuracy of each method (objective 3). This will give an indication of whether certain methods are better employed during or after treatment for breast cancer. Finally recommendations will be given for the methods to be used in breast cancer exercise research and clinical practice based on accuracy and feasibility (objective 4).

Specific hypotheses will be tested based on the literature review.

In relation to objective 1:

- H1: The HRR method will be the most accurate, and RPE the most inaccurate in the breast cancer patient group.
- H2: The intensity achieved by the RPE and MET equation methods will vary greatly from the intended exercise intensity for the breast cancer patient group.

In relation to objective 2:

- H3: The direct HR method will be the most accurate and RPE the most inaccurate in the breast cancer survivor group.
- H4: The intensity achieved by the RPE and MET equation methods will vary greatly from the intended exercise intensity for the breast cancer survivor group.

In relation to objective 3:

- H5: There will be an interaction effect between group and method accuracy.
- H6: The HR methods (both HRR and direct HR) will be more accurate in the survivor and control groups than in the patient group.
- H7: The RPE method will not differ in accuracy among the three groups.

In relation to objective 4:

- H8: The recommended method will be HRR for the patient group and the direct HR method for the survivor group.

Chapter 2: Research

Introduction

Research over the past two decades clearly demonstrates that exercise plays a significant role in cancer rehabilitation (Schmitz et al., 2010). Canadian medical and radiation oncologists are just as likely to recommend exercise to their patients as general practitioners are to sedentary asymptomatic populations (Jones, Courneya, Peddle, & Mackey, 2005). The exercise guidelines for the latter population are based on a significant amount of evidence, however, the specifics of an optimal exercise prescription that will maximize beneficial outcomes and minimize risks in the cancer population have yet to be established, and are a high priority for future research. There are four components that comprise an exercise prescription: frequency, intensity, time or duration and type (Thompson, Gordon, & Pescatello, 2010). Perhaps the most contentious, yet most important of these components is the intensity of aerobic exercise.

The significance of the intensity level of exercise in the general population is demonstrated by several research findings. First, a minimum threshold intensity above which health and fitness benefits occur has been identified (Swain & Franklin, 2002). Second, an abundance of research on interval training, which involves alternation of exercise bouts of a relatively high intensity and recovery at a lower intensity, shows numerous health, fitness and cardiac benefits (Wisloff, Ellingsen, & Kemi, 2009), many of which are substantially higher than those seen with moderate intensity exercise. Third, fitness (as measured by maximal or peak oxygen consumption (VO_{2peak})) is the strongest established prognostic marker of cardiovascular disease (Keteyian et al.,

2008), and exercise intensity is considered the most influential variable in improving VO_{2peak} (Davis & Convertino, 1975; Swain, 2005). These findings have particular relevance to breast cancer patients and survivors. Breast cancer treatment is known to contribute to: loss of exercise capacity and physical function (Thompson et al., 2010); side effects including cardiotoxicity (Bird & Swain, 2008); and comorbid conditions, such as cardiovascular disease, and its precursor, hypertension, which are common in this population before and after diagnosis (Yancik et al., 2001).

As a result of the magnitude of the variation in efficacy on improving health and fitness outcomes seen among differing levels of exercise intensity, the regulation and control of intensity is paramount to the investigation of an optimal exercise prescription. Aerobic exercise intensity is specified in a research study or exercise program by way of a prescription. The prescription consists of a target, which can be a specific heart rate, workload or subjective rating of perceived exertion (RPE), depending on the prescription method. Each prescription method is based on physiological relationships, assumptions and/ or metabolic constants that are used to determine the specific target corresponding to a desired exercise intensity, usually expressed as a percentage of VO_{2peak}, or oxygen consumption reserve (VO_2R) (the difference between VO_{2peak} and resting oxygen consumption (VO_{2rest})). The underlying principle of intensity prescription is that the achievement of the target will elicit the desired $\%VO_2R$. It should be noted that the scientific basis of exercise intensity prescription methods are complicated by prevalent breast cancer treatment side effects such as anemia, cardiotoxicity and pulmonary toxicity that alter the response to exercise.

There are no studies available in any population comparing all exercise intensity prescription methods simultaneously, and therefore it cannot be assumed that the

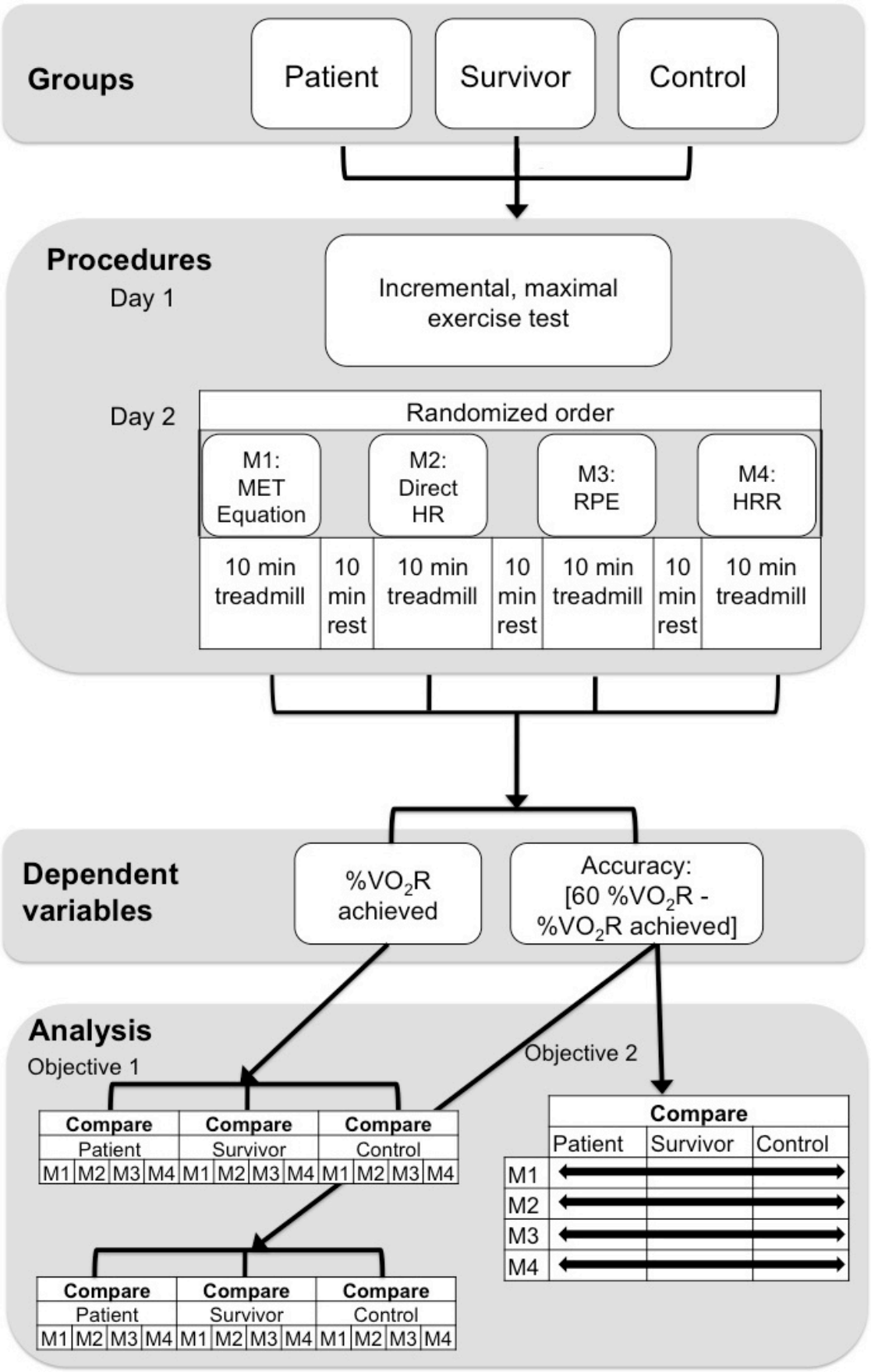
intensity, or %VO_2R achieved by each method is equivalent to each other (Thompson et al., 2010). This fact makes it difficult to compare and interpret results from studies that use different methods. The level of accuracy, or the extent to which exercise intensity prescription methods achieve the desired intensity in breast cancer populations is also unknown. Accuracy should be an important consideration in method choice, as it will affect the efficacy and safety of the exercise program implemented, whether in research or clinical practice. The ability to compare and interpret studies, and knowledge of the accuracy of different methods of intensity prescription are fundamental to the development of cancer-specific guidelines, which is a current high-priority objective in the exercise literature.

Therefore, a pragmatic, cross-sectional study was performed with the primary objective of comparing the accuracy and achieved intensity of four common methods of exercise intensity prescription within breast cancer patients, survivors and a control group. A secondary objective was to determine whether cancer treatment status (as represented by the three groups: current treatment, previous treatment or no treatment/cancer control) for breast cancer had an effect on the accuracy of these methods. Recommendations for intensity prescription method in the breast cancer population will be given, based on the results of the study, with respect to the accuracy, safety and feasibility of each method.

Methods

An overview of the study design is shown in figure 1.

Figure 1: Study design overview



Subjects

Post-menopausal women between the ages of 40-65 were recruited for one of three groups. The survivor group included women who had completed both adjuvant chemotherapy and radiation treatment for stage I-IIIA breast cancer 1-3 years prior, because this treatment combination is extremely common. The patient group included women who had completed adjuvant chemotherapy treatment for stage 1-IIIA breast cancer 2-4 weeks prior, as this treatment has the strongest potential to affect the response to exercise. The control group had no personal history of breast cancer. Post-menopausal status (not experiencing menstrual periods for at least three months) and a narrow age range were chosen in attempts to decrease variability in the physiological response to exercise seen due to hormone levels and aging. Other inclusion criteria included self-report of at least moderate physical activity in the last month (30 minutes of moderate intensity exercise, 3 times per week) to ensure their safe completion of the study protocol, and ability to understand and provide written informed consent in English. Exclusion criteria for all subjects included presence of any other major illness or disease, use of medications that alter the heart rate response to exercise (i.e. β-blockers), as well as any medical contraindications to exercise.

Ten women were recruited for each group. The women recruited for both cancer groups were past subjects in exercise intervention studies in our research laboratory. This particular group was selected because these individuals had prior experience performing cardiopulmonary maximal incremental exercise tests (of identical protocol as the current study), exercising on a treadmill, using a heart rate monitor and familiarity with the rating of perceived exertion (RPE) scale. Selection of an experienced sample was intended to reduce the influence of confounding variables, such as anxiety, or

unfamiliarity with RPE and heart rate variables. A study poster was placed in the exercise research facility to recruit study participants, and all past eligible participants were mailed a letter explaining the study. Control subjects were recruited via study posters placed at local community centres and word of mouth. On completion of the study, all subjects were offered an individualized, basic, aerobic exercise prescription based on the results of their exercise test and personal preference of intensity prescription method. The author designed the exercise programs. The study received ethical approval from the Clinical Research Ethics Board at The University of British Columbia (see appendix B).

Procedures

All testing took place over two days in the Exercise Physiology Laboratory of the Allan McGavin Sports Medicine Clinic at the University of British Columbia in Vancouver, BC, Canada. Subjects were asked to abstain from strenuous exercise for 24 hours, alcohol and nonprescription drugs for 12 hours, caffeine for 4 hours and food for 1 hour prior to both days of testing.

Subjects signed an informed consent, a Physical Activity Readiness Questionnaire (Canadian Society of Exercise Physiology, Ottawa, ON) and were asked questions regarding their diagnosis, treatment, menopausal status, physical activity and experience with treadmills and the Borg scale (either version). Seated resting heart rate and blood pressure were obtained prior to testing on both days, using a Polar A3 heart rate monitor (Polar Electro Canada Inc., Lachine, QC), sphygmomanometer and stethoscope.

Day 1: Incremental exercise test

Equipment: Subjects completed an incremental, maximal exercise test on a Precor USA c964i treadmill (Precor USA, Helsinki, Finland) with cardiopulmonary measurements collected with a Parvo Medics' TrueOne 2400 cart (Parvo Medics, Sandy, UT) and Hans Rudolph pneumotach (Hans Rudolph, Shawnee, KS). The gas analyzers of the metabolic cart were calibrated before each test and verified immediately after using primary standard gases. Volume measurement was calibrated using a 3L calibration syringe at flow rates between 40 L/min and 400 L/min.

Protocol: The incremental exercise test protocol consisted of a constant walking speed, determined during the 5-minute warm-up preceding the test, and a 1% grade to start, followed by an increase of 2% at the end of every 2-minute stage. The speed was chosen jointly by the subject and the investigator, based on elicitation of natural walking biomechanics (as opposed to a walk-run transition), and a feeling of a comfortable, but strong pace, intended to produce a test length of 8 to 15 minutes. Expired gases and heart rate were collected, analyzed and averaged over 15-second periods. The subjects were presented with Borg's category 15-point scale (see appendix A) during the last 15 seconds of each stage and at, or just after test termination, and were asked to indicate, by pointing, their current level of exertion. The indicated value was verbally confirmed by the investigator. Subjects were given standardized instructions on the use of the RPE scale prior to the exercise test (see appendix A). Subjects were not allowed to hold on to hand rails, and were verbally encouraged throughout the test. A pre-determined signal was used to indicate subjects' desire to terminate the test when they either reached volitional exhaustion or experienced any of the following symptoms: chest pain, dyspnea, dizziness, nausea, or leg cramps. A 5-minute cool-down on the

treadmill with continued monitoring of heart rate followed the test. Successful attainment of VO_{2peak} was classified as achievement of three out of four criteria of: volitional exhaustion, occurrence of a 15-second plateau in VO_2 concurrent with increased workload, a respiratory exchange ratio (RER) greater than 1.1, maximal heart rate within 5 beats per minute of the age-predicted maximal heart rate (HR max = 206.9 – (0.67*age) (Gellish et al., 2007)).

Day 2: Comparison of methods of aerobic exercise intensity prescription

The comparison of four common methods of aerobic exercise intensity prescription took place between two and 14 days after the exercise test. The four methods compared were the American College of Sports Medicine's (ACSM) metabolic equation for treadmill walking (MET equation), the direct measured relationship between heart rate and VO_2 (direct HR), the heart rate reserve (HRR) or Karvonen method, and the rating of perceived exertion (RPE) method. Each method was used to prescribe an exercise intensity of 60 %VO_2R during a 10-minute bout of exercise on the treadmill. The details of how these methods were used to prescribe exercise intensity in this study, including the variables used, classified by the day of data collection that they were obtained, the type of target (i.e. heart rate, RPE or workload) for each method and the procedure used for calculating the target corresponding to 60 %VO_2R for each method is described in table 1. All data required for use of each method was collected from the exercise test, except for resting oxygen consumption and resting heart rate (see appendix A for procedures), which were collected immediately prior to the comparison of the four methods.

Table 1: Details of how each method was used to prescribe an exercise intensity of 60 %VO_2R

Method	Variables		Exercise bout target	Equation or method for acquiring target
	Day 1	Day 2		
MET Equation	S: treadmill test speed	TVO_2, VO_{2rest}	Grade (G)*	ACSM metabolic equation for treadmill walking: $TVO_2 = 2.68*S + 48.2*S*G + VO_{2rest}$; solve for G
HRR	HR_{max}	HR_{rest}	Target HR (THR)	$THR = (HR_{max} – HR_{rest})*0.60 + HR_{rest}$
Direct HR	15-second averaged HR and VO_2 values from test	TVO_2	Target HR (THR)	A regression was created from the 15-second averaged HR and VO_2 values from the exercise test for each subject and was solved for the THR corresponding to the TVO_2.
RPE	The RPE and corresponding VO_2 values for the last 15 seconds of each stage of test, plus the last value before test termination	TVO_2	Target RPE (TRPE)	A regression was created from the RPEs and corresponding 15-second averaged VO_2 values from the exercise test for each subject and was solved for the RPE corresponding to the TVO_2.

*Treadmill test speed is chosen, not calculated, but is also used in target.
TVO_2 = target $VO_2 = (VO_{2max} – VO_{2rest})*.60 + VO_{2rest}$; VO_{2max} from day 1, VO_{2rest} from day 2.
Units: VO_{2max}, VO_{2rest} and TVO_2: mL/kg/min; S: miles per hour; G: fractional incline; HR_{max}, HR_{rest} and THR: beats per minute; RPE: unitless.

The methods were performed in a randomized order generated from a random number generator (Research Randomizer, www.randomizer.org). Expired gases and heart rate were collected during each bout with the Parvo Medics' TrueOne 2400 cart to give an accurate measurement of the exercise intensity (%VO_2R) achieved by each method (Crouter, Antczak, Hudak, DellaValle, & Haas, 2006). A warm-up and ramp to achieving the target for each method was performed within the first 5 minutes of each bout. The target was held for the last 5 minutes of the bout. The achieved intensity of each method is an average of the %VO_2R of the last five 1-minute averaged values of the exercise bout only. The accuracy of the methods was defined as the absolute value

of the difference between the intended 60 %VO_2R and the achieved intensity during the last 5 minutes.

There was a minimum 10-minute rest in between each exercise bout, where subjects were encouraged to sit in front of a fan and hydrate, in attempts to prevent cardiovascular drift after the first bout (Hamilton, Gonzalez-Alonso, Montain, & Coyle, 1991). The next exercise bout was not started until the subject achieved a seated heart rate within 5-10 beats of their resting heart rate. Whenever possible the heart rate achieved was within 5 beats or less, but this was not possible for a few subjects, even with 20-25 minutes rest or more.

All methods were used in a way that closely approximated the way they would be used in practice in a research or clinical setting. However, due to the equipment (mouthpiece, pneumotach and tubing) that the subjects were required to wear, it was difficult for the subjects to change the treadmill grade and speed themselves, so adjustments were made by the investigator as necessary. In both the heart rate methods (direct HR and HRR), the treadmill speed and grade were manipulated by the investigator to achieve the target heart rate during the first five minutes of the bout, and was adjusted thereafter as needed to maintain the target when the subject's heart rate fluctuated on the Polar A3 heart rate monitor by more than +/- three beats of the target. The subject was allowed to wear a heart rate monitor watch for both the heart rate methods and the MET equation method bouts. In the MET equation method bout, the treadmill grade and speed were gradually increased to reach the target speed and grade within the first 5 minutes, where it remained until the end of the bout. In the RPE method bout, Borg's scale was visible to the subject with an arrow pointing to their target RPE. The treadmill speed and grade were adjusted by the investigator as per

input from the subject via pre-determined hand signals, and the target was achieved before the end of the first five minutes. Thereafter, to maintain the target, the subject was instructed to indicate their desire for a change, and was additionally probed at least twice during the remaining five minutes of the bout, as to whether they were still at their target. If the RPE was not the first bout, the subject was instructed to base their perceived exertion on the Borg scale only, and to disregard the exertion experienced during any of the previous bouts. Following the initial two bouts, the Parvo Medics cart tubing and filter were changed, the mixing chamber was dried, and the gas analyzers were recalibrated. The treadmill speed and grade were covered from view of the subject for all four of the bouts.

Statistics

Analysis for age, anthropometric and physiological characteristic differences among the three groups was performed by ANOVA. To ensure that there were no differences in the number of beats above resting heart rate achieved before beginning each method across the three groups and the four methods, a 3 x 4 ANOVA was performed. A comparison of the accuracy, defined as the absolute value of the difference between 60 %VO_2R and the achieved VO_2R ([60 %VO_2R – achieved %VO_2R]) within each group was analyzed with a one-way ANOVA for each group independently. The average achieved %VO_2R by each method was compared with a one-way ANOVA for each group independently. For these three analyses, Tukey's HSD test was used when variances were homogeneous, and Games-Howell test was used when they were not, as it does not assume homogeneity of variance (Field, 2009). . The interaction of cancer treatment status (current-patient, previous-survivor, none-control) and method accuracy was analyzed with a 3 x 4 ANOVA. The distributional

assumptions required for ANOVA were considered for all tests. First, independence between methods was assumed for each subject because the subjects were required to recover to within 5 beats of their resting heart rate before beginning the next method, hence returning them to baseline. Second, equality of variance was tested with Levene's statistic. When this assumption was violated, the Welch statistic is reported as it is preferred because it controls the type I error rate well (Field, 2009). Third, the normality assumption was tested by the Shapiro-Wilk test. Any unmet assumptions are discussed in the results. The alpha level was set at p=.05 for all analyses, unless otherwise indicated. All data was analyzed with PASW (formerly SPSS) version 18.0.

Results

Subjects

Table 2 shows a comparison of the age, anthropometric and physiological characteristics collected for each group. There was a statistically significant difference in age between the patient (M=47.7, SD=3.7) and the control groups (M=54.3, SD=4.5), p<.01. The post-menopausal status inclusion criteria is the likely reason for this difference, as the cancer groups are more likely to be post-menopausal at an earlier age, due to chemotherapy. The 6.6 year difference between the groups is not likely to affect the results of the study. The only anthropometric difference between the groups revealed in post hoc analysis was height between the survivor (M=1.68 m, SD=0.1) and the control (M=1.58 m, SD=0.1) groups, p=.01. Weight differences between these groups (M=78.6, SD=17.5, M=65.0, SD=14.1, respectively) approached significance, p=.10, yet body mass index (BMI) did not differ, p=.67, suggesting that the survivor group was physically larger overall. The differences in VO_{2peak} and VO_{2rest} did not reach

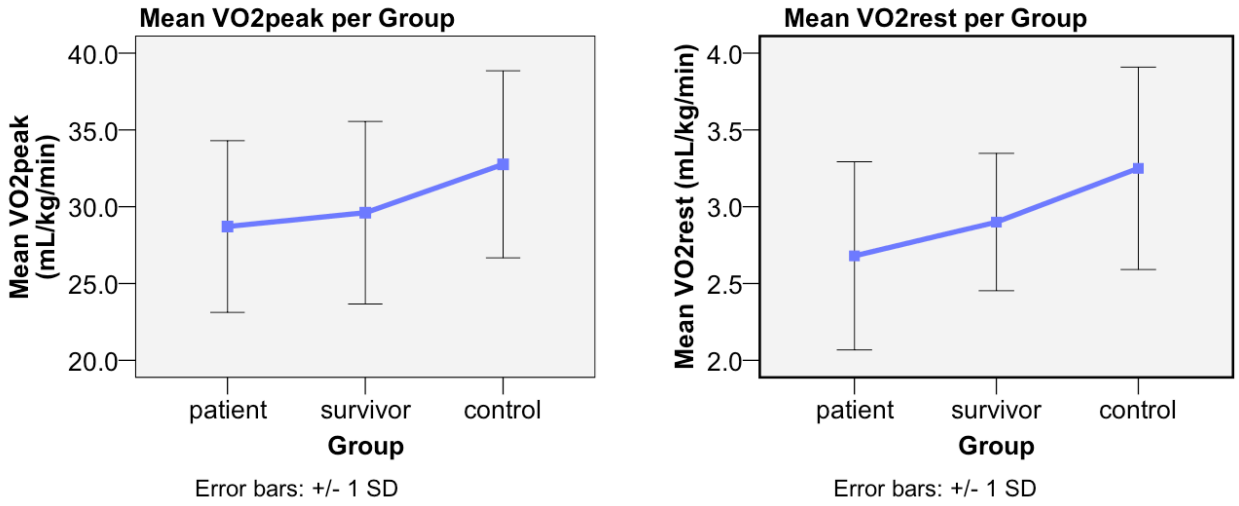
statistical significance but a similar relationship is seen in their group means, as shown in figure 1.

Table 2: Age, anthropometric and physiological characteristics of each group, with ANOVA significance.

	Patient	**Survivor**	**Control**	**P-value**
Age (years)	47.7±3.7*	52.0±5.7	54.3±4.5*	*.01
†Weight (kg)	65.7±9.2	78.6±17.5	65.0±14.1	.07
Height (m)	1.66±0.1	1.68+0.1*	1.59±0.1*	*.02
†BMI (kg/m^2)	23.9±2.6	27.8±5.1	25.8±6.3	.22
Relative VO_{2peak} (mL/kg/min)	28.7±5.6	29.6±5.9	32.8±6.1	.29
Absolute VO_{2peak} (L/min)	1.89±0.5	2.25±0.3	2.08±0.3	.13
VO_{2rest} (mL/kg/min)	2.7±.6	2.9±.5	3.3±.7	.11
†HR_{rest} (bpm)	69±10	61±7	64±8	.12
HR_{max} (bpm)	172±16	174±9	180±7	‡.15
†HRR	103±17	113±14	116±7	‡.10
†Systolic blood pressure (mmHg)	109±11	117±11	116±12	.28
†Diastolic blood pressure (mmHg)	73±7	79±10	77±4	‡.21
Attainment of VO_{2peak} (count)	7	9	9	n/a

† Reported values are those obtained on day 2 of data collection.
* Significant for alpha level of .05, denotes differing groups.
± Indicates standard deviation.
‡ Reported p-value is from Welch statistic, as data exhibited normal distribution but heterogeneous variances.

Figure 2: Comparison of the mean VO_{2peak} achieved, and the mean VO_{2rest} for each group.



Although the group differences were not significant, the general trend for both variables is that the patient group exhibited the lowest values, the survivor group had slightly higher values and the control group values were quite a bit higher than both groups, implying potential differences in metabolism and aerobic fitness among the groups. Note that the difference in the two scales is 10-fold.

Table 3 provides the cancer and treatment characteristics of the two cancer groups. Table 4 describes the self-reported exercise habits during the one month previous to data collection of the three groups. In describing the average intensity of their exercise, the subjects were asked “how hard would you say your exercise is, easy, moderate or hard?” Note that this information is provided for description of the study sample only, and may not be indicative of the populations to which the groups belong, as the patient group had just completed an exercise intervention study with prescribed exercise, and the survivor group had previously completed the study as well. The control group’s experience with treadmill use, the Borg scale and heart rate monitors is listed in table 5 to give an indication of the extent to which inexperience may have been a confounding variable in this group.

Table 3: Cancer and cancer treatment characteristics

Characteristic		Patients	Survivors
Cancer diagnosis			
Stage	I	3	1
	II	3	3
	III	2	5
	Undetermined	2	1
Side	Left	6	5
	Right	5	5
Elapsed time	Since diagnosis (months)	7±2	26±4
Surgery			
Type	Mastectomy	5	6
	Lobectomy	5	6
Nodes	Removed (#)	7±6	9±8
	Positive (#)	1±2	4±7
Elapsed time	Since surgery (months)	6±1	24±5
Chemotherapy			
Chemotherapy protocol	AC	1	0
	ACT	0	1
	ACTG	1	1
	ACTT	1	
	ACTTG	1	1
	DC	2	1
	FECD	4	5
	FECDT	0	1
Elapsed time	Since last treatment (weeks)	3.5±0.5	87.5±20.9
Radiation			
Timing	Current	3	0
	Past	0	10
Hormonal therapy			
	Currently receiving hormonal therapy	0	9
Type	Aromatase inhibitor	0	5
	Selective estrogen receptor modulator	0	4
Biological therapy (monoclonal antibody)			
Timing	Current	2	0
	Past	0	2

Where not indicated, data is count data.
Note: in cases where total count exceeds n, subjects in that group experienced more than one of the conditions.

Table 4: Self-report of average exercise habits in the one month previous to data collection

Descriptor	Patients	Survivors	Controls
Frequency (average/week)	3.4	3.9	5.0
Intensity (mode)	Moderate	Moderate	Moderate
Duration (average in min)	38	51	49

Table 5: Experience variables of control group (percentage of total)

Treadmill use in past year				Familiar with Borg scale	Heart rate monitor use in past five years
0x	1-3x	4-12x	12+x		
30%	10%	30%	30%	30%	50%

Equivalency in number of beats above resting heart rate between methods and groups

The interaction effect, $F(6,101)=.62$, $p=.71$, group main effect, $F(2,101)=.39$, $p=.68$, and method main effect, $F(3,101)=.58$, $p=.63$ were all non-significant, indicating that the number of beats above resting heart rate before beginning each method was the same across all levels of method and group. The average number of beats above resting by method and group are listed in table 6.

Table 6: Average number of beats per minute above resting heart rate before beginning exercise bout.

Method	Patient	Survivor	Control
MET Equation	4	4	3
Direct HR	3	5	5
RPE	5	3	5
HRR	3	4	4

Accuracy of each method within each group

Table 7 lists the descriptive statistics of the accuracy by group and method. The units used for accuracy are percentage points (ppts), the arithmetic difference between two percentages. Note that the with the HRR and direct HR methods, when it took

longer than 5 minutes to achieve the target heart rate, an extra equivalent amount of time was added to the total bout length. For example, if it took 6 minutes to reach the target, then the bout lasted 11 minutes instead of 10. A maximum of 2 extra minutes were added in any case. The $\%VO_2R$ achieved was always taken as the last 5 minutes of the bout.

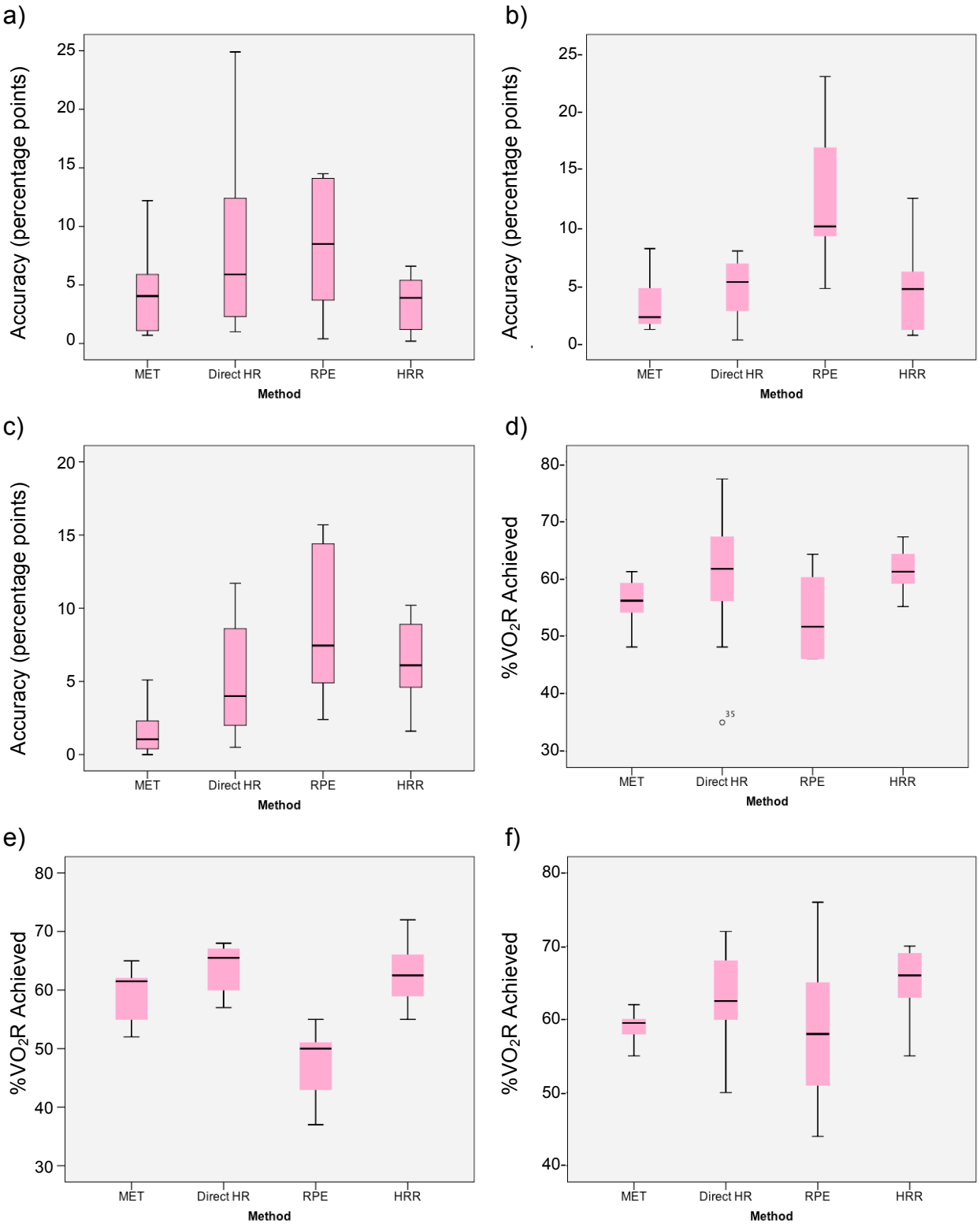
Patient group

For the patient group, the assumption of homogeneity of variance was not met, $F(3,36) = 3.94$, $p=.02$, as demonstrated in figure 2a). However the assumption of normality was not violated for any of the methods (MET equation, $p=.17$, direct HR, $p=.14$, RPE, $p=.42$, HRR, $p=.35$). Therefore, the Welch statistic and Games-Howell tests were used for significance testing and post hoc analysis respectively. The Welch statistic was significant, $F(1,18.6) = 3.45$, $p=.04$. The only two methods that differed significantly in their accuracy were the RPE method ($M=9$, $SD=5$) and the HRR method ($M=3$, $SD=2$), $p=.05$.

Table 7: Descriptive statistics of the accuracy (absolute value of difference between 60 %VO_2R and intensity achieved, expressed in percentage points) of each method within each group

	Patient	Survivor	Control
MET equation			
Average	4	3	2
Standard Deviation	4	2	2
Maximum	12	8	5
Minimum	1	1	0
Range	11	7	5
Direct HR			
Average	8	5	5
Standard Deviation	8	2	4
Maximum	25	8	12
Minimum	1	0	1
Range	24	8	11
RPE			
Average	9	13	9
Standard Deviation	5	6	5
Maximum	15	23	16
Minimum	0	5	2
Range	15	18	14
HRR			
Average	3	5	6
Standard Deviation	2	4	3
Maximum	7	12	10
Minimum	0	1	2
Range	7	11	8

Figure 3: Boxplots of the accuracy and achieved intensity by method and group



a) patient group accuracy; b) survivor group accuracy; c) control group accuracy; d) patient group achieved intensity; e) survivor group achieved intensity; f) control group achieved intensity

Survivor group

For the survivor group the assumption of homogeneity of variances was violated as well, as seen in figure 2b), $F(3,36)=5.31$, $p<.01$, and the normality assumption was not violated for any of the methods (MET equation, $p=.07$, direct HR, $p=.63$, RPE, $p=.26$, HRR, $p=.11$). The Welch statistic and Games-Howell tests were used for significance testing and post hoc analysis respectively. The Welch statistic was significant, $F(3,19.2)=6.89$, $p<.01$. The RPE method ($M=13$, $SD=6$) differed significantly in accuracy from all three methods (MET equation: $M=3$, $SD=2$, $p<.01$; Direct HR: $M=5$, $SD=2$, $p<.01$; HRR: $M=5$, $SD=4$, $p=.01$).

Control group

The control group followed a similar pattern in violation assumptions, the assumption of homogeneity of variances was violated, $F(3,36)=5.29$, $p<.01$, as seen in figure 2c), but the normality assumption was not for any of the methods (MET equation, $p=.15$, direct HR, $p=.25$, RPE, $p=.19$, HRR, $p=.71$). Therefore, the Welch statistic and Games-Howell tests were used again. The Welch statistic was significant, $F(3,18.4)=11.13$, $p<.01$. The MET equation method ($M=2$, $SD=2$) differed significantly from both the RPE method ($M=9$, $SD=5$), $p<.01$, and the HRR method ($M=6$, $SD=3$), $p<.01$.

Achieved intensity of each method within each group

Table 8 lists the descriptive statistics of intensity achieved by group and method.

Patient group

For the patient group, there was one outlier, defined in the PASW software as a value larger than 1.5 times the interquartile range, in the direct HR method, as

indentified by the boxplot in figure 2d). The outlier was removed for the inferential analysis. The one-way ANOVA was significant, $F(3,35) = 5.40$, $p < .01$. Post hoc analysis revealed that the RPE method (M=53, SD=7) achieved a significantly different intensity than both the direct HR (M=60, SD=12), $p<.01$, and HRR (M=61, SD=4), $p=.02$ methods. The difference between the MET equation method (M=56, SD=2) and the direct HR method also approached significance ($p=.09$).

Table 8: Descriptive statistics of achieved intensity (%VO_2R) of each method, within each group

	Patient	**Survivor**	**Control**
MET Equation Method			
Average	56	59	59
Standard Deviation	2	4	2
Maximum	61	68	62
Minimum	48	57	55
Range	13	11	7
Direct Heart Rate Method			
Average	60	64	63
Standard Deviation	12	4	6
Maximum	77	68	72
Minimum	35	57	50
Range	42	11	22
Rating of Perceived Exertion Method			
Average	53	47	58
Standard Deviation	7	6	10
Maximum	64	55	76
Minimum	46	37	44
Range	18	18	31
Heart Rate Reserve Method			
Average	61	63	65
Standard Deviation	4	6	5
Maximum	67	72	70
Minimum	55	55	55
Range	12	18	15

Survivor group

For the survivor group, there were no outliers, as indicated by the boxplot in figure 2e). The one-way ANOVA was significant, $F(3,36)=23.26$, $p<.01$. Post hoc analysis revealed highly significant differences in intensity achieved between the RPE method (M=47, SD=6) and all three of the other methods (MET equation: M=59, SD=4; direct HR: M=64, SD=4; HRR: M=63, SD=6), all at $p<.01$).

Control group

For the control group, there were no outliers, as indicated by the boxplot in figure 2f). The homogeneity of variance assumption was not met, as indicated by Levene's test, $T = 7.62$, $p<.01$. Yet, the normality assumption was met for each of the methods (MET equation, p=.68, direct HR, p=.86, RPE, p=.61, HRR, p=.08). Therefore, the Welch statistic and Games-Howell test were used to test for significance and post hoc analysis respectively. The Welch statistic was significant, $F(3,17.2)=4.40$, $p=.02$. The MET equation method (M=59, SD=2) achieved a significantly different intensity than the HRR method (M=65, SD=5), p=.02.

Cancer treatment status by method accuracy interaction

Levene's test indicated that the homogeneity of variances assumption was violated, $F(11,108)=4.08$, $p<.01$. The nonparametric tool available to test a two-way ANOVA does not calculate a p-value for the interaction effect. One objective of the study was to determine whether cancer treatment status affected method accuracy, as would be determined by analyzing the interaction effect between the two variables; therefore, the violation of the homogeneity of variance assumption was tolerated. The interaction effect was significant, $F(6,108) = 2.37$, $p=.04$, partial eta squared = .12, a

medium to large effect, indicating that the exercise intensity prescription methods did not have the same accuracy across all three groups. To investigate the interaction further, a posteriori contrasts were planned from figure 3. The details of the hand calculations are provided in table 9. The Bonferroni method was used to adjust the pair-wise alpha to p=.013, in order to keep the experiment-wise alpha at p=.05, so the critical F-value was determined for an alpha of .01. The calculated F-value for contrasts 2, F(2,108)=7.71 and 3, F(2,108)=11.76 exceeded the critical F(2,108)=4.81 at alpha level of .01. Therefore, cancer treatment status affected the accuracy of the direct HR and RPE methods only. Contrasts 1, F(2,108)=3.92, and 4, F(2,108)=4.21 did not exceed the critical F-value, and hence the accuracy of the MET equation and HRR methods were not affected by cancer treatment status.

Figure 4: Comparison of the accuracy of each method by group

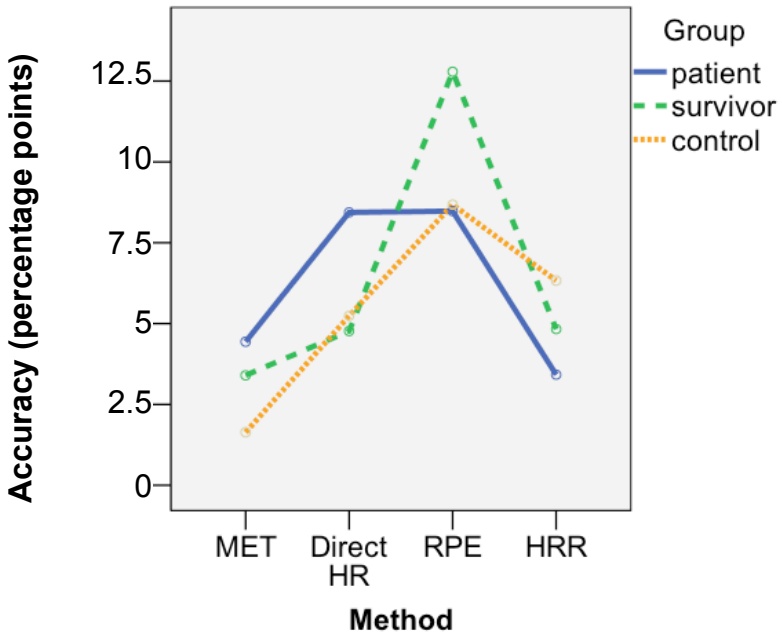


Table 9: A posteriori contrasts used to further investigate the cancer treatment status by method accuracy interaction

#	Method	Patient	Survivor	Control	Calculation	Sig. for F > critical F*
		Contrast coefficients				
1	MET Equation	1	0	-1	$\Psi_1 = F_{(2,108)} = \frac{[(1*.044)+0+(-1*.016)]^2}{.001*\left(1^2/10+0+-1^2/10\right)} = \frac{.000784}{.0002} = 3.92$	No
2	Direct HR	1	-0.5	-0.5	$\Psi_2 = F_{(2,108)} = \frac{[(1*.084)+(-.5*.048)+(-.5*.052)]^2}{.001*\left(1^2/10+-.5^2/10+-.5^2/10\right)} = \frac{.001156}{.00015} = 7.71$	Yes
3	RPE	0.5	-1	0.5	$\Psi_3 = F_{(2,108)} = \frac{[(.5*.085)+(-1*.128)+(.5*.087)]^2}{.001*\left(.5^2/10+-1^2/10+.5^2/10\right)} = \frac{.001764}{.00015} = 11.76$	Yes
4	HRR	1	0	-1	$\Psi_4 = F_{(2,108)} = \frac{[(1*.034)+0+(-1*.063)]^2}{.001*\left(1^2/10+0+-1^2/10\right)} = \frac{.000841}{.0002} = 4.21$	No

Mean square error of .001 is taken from ANOVA results for group main effect.
*Critical F(2,108)=4.81 at alpha level of .01

Discussion

There were three objectives of the study: 1) to determine how the accuracy of and intensity achieved by four common methods compared in breast cancer patients, survivors and a control group; 2) to determine whether current treatment, previous treatment or no treatment for breast cancer had an effect on the accuracy of these methods; and 3) to give recommendations for method use in breast cancer populations with respect to the accuracy and feasibility of each method. The descriptive and inferential statistical results are used to discuss the outcomes resulting from each objective.

Accuracy and achieved intensity of each method within each group

Patient group

In the patient group, the only significant difference in accuracy was between the HRR (3 ppts) and RPE (9 ppts) methods, although the MET equation and direct HR methods only differed by 1 ppt from these two, respectively. The RPE method had the lowest achieved intensity at 53 %VO_2R, which differed significantly from both the HRR (61 %VO_2R) and direct HR (60 %VO_2R) methods. The average accuracies of 4 and 3 ppts and average achieved intensities of 56 and 61 %VO_2R for the MET equation and HRR methods respectively, indicates that they are reasonably accurate in this population. The RPE method was the least accurate and achieved the lowest intensity of the four methods. Although the direct HR method achieved an average intensity of 60 %VO2R, the accuracy was comparably low to the RPE method at 8 ppts.

The use of measured VO_{2rest} rather than the constant value of 3.5 mL/kg/min in the ACSM's metabolic equation likely increased the accuracy of the MET equation method, as there was a trend toward significance (p=.11) in the difference of measured VO_{2rest} values between the groups, with the patient group differing most from the control group (table 2).

The ACSM has adopted %HRR and %VO_2R as the primary means of establishing exercise intensity in their 1998 position stand on recommended exercise quality and quantity (Pollock et al., 1998). It has been demonstrated that %HRR more closely approximates %VO_2R than %VO_{2max} in healthy (Swain & Leutholtz, 1997), heart disease patient (Brawner, Keteyian, & Ehrman, 2002), diabetic (Colberg, Swain, & Vinik, 2003), obese (Byrne & Hills, 2002) and elite cyclist (Lounana, Campion, Noakes,

& Medelli, 2007) populations, but has not yet been investigated in cancer populations. The accuracy of the HRR method to prescribe exercise intensity was actually the highest (3 ppts), with lowest range in achieved intensities (12 %VO_2R) in the patient group, compared to the other two groups.

The direct HR method uses the direct relationship between heart rate and VO_2 as determined for each individual, and is recommended for use in individuals who may not exhibit a one-to-one relationship between the variables, such as those with low fitness levels, those with cardiovascular or pulmonary disease, or those with an altered heart rate response to exercise (Whaley, Brubaker, & Otto, 2006). Although the incidence of chemotherapy-induced heart disease is fairly low, there is a high potential for less severe damage to go unnoticed and affect heart function (Ewer & Lenihan, 2008). Associated outcomes of chemotherapy-induced cardiotoxicity include decreased myocardial contractility leading to decreased stroke volume and reduced ability to increase stroke volume in response to exercise, causing an associated increase in heart rate at rest and during submaximal exercise. Chemotherapy treatment for breast cancer can also cause pulmonary toxicity (Yerushalmi et al., 2009). Anemia, which occurs in 30-90% of cancer patients (Wade et al., 2004) will cause an altered heart rate response to exercise. These factors suggest that the direct HR method of prescribing exercise intensity might be an appropriate choice for individuals who have recently completed chemotherapy treatment. However, the results of this study indicate that it is the least accurate out of the three methods that use objective physiological data, with an average of 8 ppts and standard deviation of 8 ppts. While the intensity achieved by this method in the patient group averaged 60% VO_2R, the range of intensities achieved within the group was very large at 42 %VO_2R.

The 15-point Borg scale used in this study was constructed to increase linearly with exercise intensity similar to the linear increase in heart rate and VO_2 (Borg, 1982). Perception of exertion has been shown to be a better predictor of VO_{2max} than heart rate, suggesting that despite an increase in heart rate relative to VO_2, RPE would continue to serve as guide to exercise intensity (Eckblom & Golobarg, 1971; Noble, 1982). RPE may be a useful method of prescribing exercise intensity in breast cancer patients, as tachycardia and bradycardia both commonly occur as side effects of chemotherapy for breast cancer (Bird & Swain, 2008). The lower accuracy of the RPE method (9 ppts) in this study does not negate the usefulness of the method for the aforementioned purpose, but the methods using more objective measures were all more accurate. The average intensity achieved by the RPE method was 53 %VO_2R, which was significantly lower than the intensity achieved by both the heart rate methods, indicating that the RPE method typically achieves a lower than intended exercise intensity in this group.

Survivor group

In the survivor group, the accuracy and achieved intensity of the RPE method significantly differed from all three methods. The average accuracy of 13 ppts was the lowest of any method and any group in the analysis. The other methods were more than 50% more accurate (more than twice the divergence) compared to the RPE method for the survivor group. The average achieved intensity was 47 %VO_2R, indicating that the method consistently achieved intensities lower than intended. The three other methods were all fairly accurate, ranging from 3-5 ppts of accuracy, and 59-64 %VO_2R achieved intensity. Although survivors are finished surgery, chemotherapy and radiation treatment, they may still be recovering from acute side effects, and/or experiencing late-

onset or chronic side effects from these treatments, in addition to receiving hormonal therapy for 2-5 more years. There are several potential sources of side effects that could alter the physiological response to exercise of breast cancer survivors, thereby creating potential for inaccuracy in methods relying on physiological relationships and metabolic constant values. However, these results indicate the clear advantage of using objective physiological data in this population. It is interesting to note that the two heart rate methods were similar in accuracy, and the extreme variability in achieved intensities seen in the patient group with the direct HR method was not experienced in the survivor group.

Control group

In the control group, the MET equation method was very accurate with an average accuracy of 2 ppts and average achieved intensity of 59 %VO_2R, and differed significantly from the HRR method at 6 ppts and 65 %VO_2R. The RPE method's average achieved intensity was 58 %VO_2R, but the accuracy of 9 ppts differed significantly from the MET equation method. The direct HR method was also quite accurate in this group, with an average of 5 ppts and achieved intensity of 63 %VO_2R.

The influence of using measured VO_{2rest} in place of the constant value in the MET equation is likely not as significant as with the other two groups, as the averaged measured VO_{2rest} for this group was quite close (3.3 mL/kg/min) to the constant value of 3.5 mL/kg/min (table 2). In addition, the range between intensities achieved by this method was only 7 %VO_2R (maximum = 62 %VO_2R, minimum = 55 %VO_2R), indicating that there is low variability in the metabolic cost of walking in this healthy population.

Interestingly, the range of intensities achieved by the RPE method was the largest in the control group at 31 %VO_2R, with half of the subjects achieving intensities

higher than the intended intensity. In contrast, all of the survivors, and 80% of the patients achieved intensities lower than the intended intensity and with a range of nearly half that of the control group (18 %VO_2R for both groups).

It is interesting to note that the two heart rate methods were quite similar in accuracy in the control group, but both showed a fairly large range of achieved intensities (direct HR = 22 %VO_2R, HRR = 15 %VO_2R) indicating that the heart rate methods may not be reliable in terms of achieving similar relative intensities between individuals, even in a healthy normal population.

Cancer treatment status by method accuracy interaction

MET equation method

The accuracy of the MET equation method did not vary across the three groups. A possible explanation for the lack of difference among the groups for this method is that VO_{2rest} was measured and used in the equation, in lieu of the conventional constant of 3.5 mL/kg/min. This may have reduced some of the variability in using the ACSM metabolic equation, which also uses assumed constant values for the O_2 cost of walking in addition to the VO_{2rest} constant. The average measured values of VO_{2rest} in the current study were, 2.7±.6, 2.9±.5 and 3.3±.7 mL/kg/min for the patient, survivor and control groups respectively. Another study with a similar sample (12 healthy women, average age = 40 years) reported a similar average VO_{2rest} value of 2.8±.4 (Gunn et al., 2002). The results suggest that there may be value in measuring VO_{2rest} or at least using reported values of other similar populations rather than relying on the conventional constant value.

Direct HR method

Cancer treatment status had an effect on the accuracy of the direct HR method. The survivor and control groups showed a similar average accuracy, which, when combined was significantly lower than that of the patient group. Of the three groups, the patient group is most likely to experience an altered heart rate response to exercise, due to current chemotherapy treatment. This is one of the conditions where the direct heart rate method is recommended. The results of this study indicate the direct HR method is more accurate in the survivor and control groups, who are less likely to exhibit this altered heart rate response. The inaccuracy of the direct HR method in the patient group throughout the chemotherapy duration has been previously described by our laboratory (Kirkham, Campbell, Jespersen, & McKenzie, 2009), and the current study indicates that it is inaccurate for short-term use as well.

RPE method

Cancer treatment status also affected the accuracy of the RPE method. The patient and control groups exhibited an accuracy (9 ppts) that was significantly lower than that of the survivor group (13 ppts). It is unknown why this method would differ among the two cancer groups, but a side effect of chemotherapy could offer a speculative explanation for the difference. Cancer-associated cognitive decline is reported in 17-75% of breast cancer patients as a side effect of chemotherapy (Wefel, Lenzi, Theriault, Davis & Meyers, 2004). Several of the cognitive domains affected, including memory and information processing speed, would be employed in the estimation and later production of a target RPE required in this study. A recent longitudinal study measured cognitive function at timepoints in chemotherapy treatment comparable to the two cancer groups in the current study. This study reported a decline

from baseline (prior to chemotherapy) to immediately following chemotherapy completion in 61% of breast cancer patients; 18 months after baseline half of these individuals' impairments had improved (Wefel et al., 2004). This study indicates that the there are differences in prevalence of cognitive impairments at the timepoints of treatment represented by the two cancer groups in the current study. However, the specific outcome of the effect of these impairments on the accuracy of RPE method of prescribing exercise is unclear.

There has been one study that compared breast cancer survivors' estimated RPE of an ongoing submaximal exercise intensity to that of healthy control subjects (Evans, Battaglini, Groff, & Hackney, 2009). For relative intensities of 40, 60 and 70 $\%VO_{2peak}$, survivors did not differ significantly from controls in the RPE estimates (Evans et al., 2009). Age and menopausal status were not well controlled between the groups. In the current study, subjects were required to estimate RPE during the graded exercise test, and then were asked to produce a target RPE during a 10-minute bout of submaximal exercise. It should be noted that the psychophysical process required to produce an intensity from memory is not the same as the process of estimating an ongoing intensity (Noble, 1982). A study with a similar protocol to the current study, reported statistical differences in absolute VO_2 achieved during the production trial of the RPE corresponding to 70 $\%VO_{2max}$, but not at 50 $\%VO_{2max}$ (Dunbar et al., 1992). Another reported a statistical difference in $\%VO_{2max}$ achieved with a production trial of an RPE corresponding to an intended intensity of 75 %HRR (Glass, Knowlton, & Becque, 1992). The intensity used in the current study, 60 $\%VO_2R$, is in between those investigated in these estimation-production studies, so it is unknown, but possible that the disparity in the result of RPE differences between survivor and control groups

between the current study and the study conducted by Evans et al. can be attributed to the difference in estimation versus production of RPE.

HRR method

There was not a statistically significant effect of cancer treatment status on the accuracy of the HRR method. However, review of the descriptive data of the accuracy and achieved intensity of the method within each group (tables 7 and 8) indicates that the method is the most accurate, and least variable in the patient group. Regardless of group, the lowest achieved intensity was 55 %VO_2R, indicating that this method is not likely to achieve an intensity much lower than the prescribed intensity.

Recommendations for method use

The average accuracy and/or average intensity achieved by each method alone are not a sufficient basis for recommendations stemming from the current study of the most appropriate method of exercise intensity prescription for each of the cancer groups. The standard deviation does improve the ability to describe the accuracy of each method, however, for a well-rounded interpretation of the accuracy of each method, the maximum, minimum and range are considered. The maximal and minimal achieved intensities in each group provide an indication of the amount by which that method has to the potential to overachieve or underachieve (i.e. achieve an intensity greater or lesser than the intended intensity). Tolerance for an over or underachievement of that size is then assessed for each group based on considerations of safety and primary exercise objectives to judge the appropriateness of that method for that group. Range of intensities achieved is also considered, as methods with a

large range would not be ideal in exercise intervention studies where all members of the same arm of the study are expected to be exercising at the same intensity.

All forms of treatment for breast cancer compromise immune function. The effect of aerobic exercise training on the immune system of breast cancer patients remains inconclusive (Drouin, 2002), but high intensity exercise is known to compromise the immune system in other populations (Schneider, Dennehy, & Carter, 2003). As such, a crucial factor that should be considered in the choice of an aerobic exercise intensity prescription method is the likelihood that the method will overachieve the intended intensity. This consideration is especially important in individuals currently receiving chemotherapy treatment. The main objective during chemotherapy treatment may be maintenance of fitness rather than improvement, so achieving a lower than intended intensity is less of a concern than overachievement. At the survivor stage, the priority may shift to rehabilitation, which includes a focus on gaining the optimal health and fitness benefits from exercise. The overachievement of intensity is less of a concern for individuals who have finished chemotherapy and radiation treatments, as their immune function has likely had time to recover. The recommendations for method use for the breast cancer patient and survivor groups are given with these considerations in mind.

Patient group

The HRR method was the most accurate in the patient group when considering the average, standard deviation, maximum and minimum achieved intensity (61± 4, 55-67 %VO_2R) and accuracy (3 ± 2, 0-7 ppts). All but one of the patients achieved an intensity within 5 ppts of 60%VO_2R. This method is feasible, as it would only require one maximal exercise test without expired gas analysis to determine maximal heart rate, a variable unlikely to be affected by chemotherapy. A review of exercise testing in cancer

studies indicates that maximal exercise testing is relatively safe (Jones et al., 2008). The HRR method could potentially be used effectively throughout the duration of chemotherapy by frequently adjusting the prescription with observed changes in resting heart rate. This technique requires confirmation by future research.

The MET equation method did not overachieve exercise intensity (maximum = 61 %VO_2R) and the maximal underachievement was 12 %VO_2R, and the average accuracy was 4 ppts. However, this method requires an accurate VO_{2peak} and VO_{2rest} value, which have the potential to vary if resting metabolic rate changes occur throughout chemotherapy treatment (Demark-Wahnefried et al., 1997; Harvie, Campbell, Baildam, & Howell, 2004). Therefore, to maximize accuracy, frequent maximal cardiopulmonary testing would be required with this method, which may not be feasible during chemotherapy treatment.

The RPE method underachieved the intended intensity by 14 ppts in one third (3/10) of patients, but tended not to overachieve (maximum = 64 %VO_2R). Although research indicates that RPE remains an accurate indicator of VO_2 regardless of changes in heart rate (Eckblom & Golobarg, 1971), it is unknown whether perceived exertion would vary with the other physiological alterations that may occur throughout chemotherapy treatment such as a reduction of the oxygen carrying capacity of the blood and impaired gas exchange. Therefore, the temporal accuracy of the RPE method is unknown, but remains a safe short-term option for exercise intensity prescription in breast cancer patients.

The method with the most variability by far, for any group, was the direct HR method in the patient group. Although the average achieved intensity of the group was exactly 60 %VO_2R, there was a SD of 12 %VO_2R, and overachievement of the intended

intensity as high as 17 ppts and underachievement as low as 25 ppts. The potential for high overachievement, taken together with the findings of another study indicating that the relationship between heart rate and oxygen consumption on which this method is based, changes throughout chemotherapy treatment for breast cancer (Kirkham et al.,2009), indicates that this method may not be safe or effective in breast cancer patients during chemotherapy treatment.

Survivor group

For the survivor group, the direct HR method, HRR and MET equation methods were all fairly similar in accuracy when considering the descriptive statistics of accuracy and achieved intensity. The MET equation method was the most consistent, as only one participant diverging from 60 %VO_2R by more than 6 ppts. However, unless interim re-testing is planned in the research design or exercise program, to account for changes in VO_{2peak}, the accuracy of this method would be reduced. Periodic tests throughout the exercise program to measure VO_{2peak} would be advocated (Lucía, Earnest, & Pérez, 2003).

The HRR method was fairly consistent with only 2 participants who overachieved intensity by just over 10 ppts, and an average accuracy of 5 ppts. However, the range of achieved intensities was 18 %VO_2R, which introduces a fair amount of variability in a group. The direct HR method had the same accuracy of 5 ppts as the HRR method, but had a lower range of achieved intensities (11 %VO_2R), and both maximal over and underachievement, indicating that it may be better choice in exercise intervention studies. Both heart rate methods would be appropriate for use in the survivor population, as an overachievement of intended intensity of 8-12 ppts does not create as large of a safety concern for this group compared to the patient group. The HRR

method has a significant advantage over the direct HR method in terms of feasibility, as it does not require expired gas analysis.

The accuracy of the direct HR method for long-term use may be improved by including a submaximal exercise test at set intervals throughout an exercise intervention to adjust the prescribed target heart rate to account for changes due to training. In a pilot study involving breast cancer survivors in an exercise intervention, the change in heart rate from the initial exercise test to a submaximal exercise test 10 weeks later at the same absolute workload was used to predict the required adjustment in the prescribed target heart rate to continue to achieve 60 %VO_2R (Kirkham, Neil, McKenzie, & Campbell, 2010). The required equipment for the adjustment is just a treadmill and a heart rate monitor. The inclusion of the submaximal test would increase the feasibility of the direct HR method by reducing the need for further maximal exercise tests with gas analysis to re-acquire the target heart rate corresponding to the desired intensity, which may be expensive and inaccessible.

Lastly, the RPE method, which achieved an average intensity of 47 %VO_2R, and average accuracy of 13 ppts in the survivor group, was the least accurate method, regardless of group. Furthermore, this method caused an underachievement of intended intensity in every participant in the survivor group, indicating that it is not an ideal method in this population.

Study strengths and limitations

A significant strength of the study was the design, which was developed to test the methods pragmatically. The obvious diversion from practical use of these methods is that the subject was required to wear the mouthpiece and tubing to collect the expired

gas to measure the actual exercise intensity achieved. This experience can cause anxiety, especially in individuals who have never undergone cardiopulmonary exercise testing previously. Walking on a treadmill can also cause anxiety in inexperienced individuals. Anxiety and fear are known to cause rising levels of catecholamines, which is associated with increases in heart rate (Bremner, Krystal, Southwick, & Charney, 1996). A related strength of the study is that all subjects in the cancer groups were experienced with both cardiopulmonary testing and treadmill use, thereby reducing the influence of anxiety as a confounding variable.

All four of the ten-minute bouts of exercise used to test each method of exercise intensity prescription were performed on the same day. This feature of the design reduced the influence of day-to-day variations in potential confounding variables such as hydration levels, nutrition, and stress. It could be argued however that accumulated fatigue could have confounded the results of the third or fourth methods tested. Yet this factor was controlled by randomization of the order of the methods, and by returning the subjects to near-baseline levels before testing the next method.

The inclusion of a healthy control group for comparison increases the scope of the study's contributions to the literature, by providing insight into the research question applied to a healthy population as well. Although helpful in absence of other studies, the results of the comparison of methods in this study's control group should be generalized with caution. The control group consisted of 10 healthy, post-menopausal women with an average age of 54 ± 4.5 years (minimum=46, maximum=61), who responded to a recruitment poster about an exercise study at a community centre. This group represents a narrow sample of the healthy population.

The study design also creates several limitations to the interpretation of the results. The percentage of maximal heart rate method is commonly used in all populations to prescribe exercise intensity, including breast cancer research, due to its ease of use. However, this method has several limitations, including the mismatch between exercise intensity (%VO_2R) and the percentage of maximal heart rate. Because this method is used without regard for a desired VO_2, it could not be compared in its ability to achieve a desired %VO_2R, was therefore not compared in this study.

Another limitation created by the study design is that the accuracy of the methods in achieving just one intensity level was tested. Every additional intensity level tested would have required four more bouts of exercise, which would greatly decrease the feasibility of subject recruitment. The intensity level of 60 %VO_2R was chosen because it is at the borderline of moderate and hard intensity classifications (Pollock et al., 1998), and it is commonly used and recommended in exercise prescriptions for cancer patients. More research is needed to confirm the applicability of our findings to other exercise intensities.

The cross-sectional design of the study is convenient for the purposes of comparing the three groups, but does not provide any information regarding the accuracy of these methods over time. This limitation is especially applicable to the patient group, as side effects of chemotherapy treatment may be cumulative and progress in severity over time. For example, the cumulative dose-dependent effect of a common type of breast cancer chemotherapy drug, anthracyclines, suggest that damage to the heart could potentially start with the first treatment and then progressively increase with each additional treatment (Ewer & Lenihan, 2008). There is evidence to support a linear relationship between dose and amount of damage (Bristow,

Mason, Billingham, & Daniels, 1981), which suggests an incremental decline in cardiac function throughout the chemotherapy regimen. In which case, the outcome for exercise metabolism is that the relationship between heart rate and VO_2 may incrementally change throughout the course of treatment, thereby continually changing the $\%VO_2R$ achieved by the same target heart rate or workload. Similarly, an individual who has completed chemotherapy treatment may gradually recover from the side effects with concurrent changes in metabolism. Ultimately, this speculation requires further investigation.

Study implications

This study was the first to simultaneously compare four common methods of exercise intensity prescription. The results of the study can be referenced for future research involving exercise interventions or clinical practice involving breast cancer patients during chemotherapy, and survivors following completion of initial treatment foremost, as well as healthy middle-aged women, and potentially other cancer populations and other healthy demographics. The results can also be used in comparing the intensities prescribed in previous research, for the purposes of creating safe and effective exercise intensity guidelines.

Beyond one study that cross-sectionally compared cardiovascular parameters at rest and maximal exercise between breast cancer survivors and healthy controls (Jones et al., 2007), and one that compared the relationship between heart rate and VO_2 before and immediately after chemotherapy treatment for breast cancer (Kirkham et al., 2009) there has been no investigation of the exercise response in the breast cancer population that is underlying the prescription methods tested in this study. This study

indirectly suggests differences in exercise physiology among those who have recently received chemotherapy, those who have completed initial treatment for breast cancer and healthy controls. Future studies are needed to directly describe and quantify alterations in the response to exercise throughout the continuum of breast cancer, from diagnosis, throughout treatments and throughout recovery and rehabilitation after treatment. Breast cancer exercise programs will be more effective if they are based on empirical evidence, rather than existing knowledge of exercise physiology in other populations.

Conclusion

In breast cancer patients who have recently finished chemotherapy, the HRR and MET equation methods of prescribing exercise intensity appear to be accurate in achieving a desired exercise intensity of 60 %VO_2R. Unless frequent re-testing occurs, the HRR method may be preferred in this group, as the MET equation method requires accurate values of VO_{2peak} and VO_{2rest}, which can change throughout chemotherapy treatment. The RPE method seems to be a fairly safe choice in this group, as it tends to not overachieve the desired intensity. The direct HR method was extremely variable in this group, with large over and underachievements of desired intensity, and thus may not be an appropriate choice.

In breast cancer survivors who have completed chemotherapy and radiation treatment, the RPE method is much less accurate than any of the three other methods, and can drastically underachieve the desired intensity. The MET equation achieved the desired intensity most accurately and consistently in this group, but requires frequent

re-testing to account for changes in VO_{2peak}. Both the direct HR and HRR methods would be appropriate for use in this group as well.

In the healthy control group, the MET equation method was extremely accurate and had very little variability. Accuracy was comparable between the direct HR and HRR methods, and although less than the MET equation method, were both reasonably accurate, but the moderate sized range of achieved intensities should be considered when using these methods. There was a large amount of variability in the RPE method in both accuracy and intensity achieved.

Cancer treatment status had an effect on the accuracy of the methods. The direct HR method was significantly less accurate in the patient group than the survivor and control groups. The RPE method was significantly less accurate in the survivor group than the patient and control groups. Future research is needed to investigate the mechanisms underlying the differences in accuracy among these three groups.

Chapter 3: Conclusion

Potential applications of thesis research

The overall significance of this research is that it is the first study to simultaneously compare the intensity achieved and accuracy of four common methods of exercise intensity prescription in any population. Previous to this study, it was unknown how the intensity achieved by each of the methods compared to one another, or how accurate the methods were when used in practice. The results of the study provide empirical evidence to fill in the gap that was previously held by assumptions of the accuracy of these methods.

Substantial error in measurement and methods of estimating exercise is implicated in the underestimation of the effect of exercise on outcomes measured in cancer exercise studies (Ballard-Barbash et al., 2002). The need for more objective measures of exercise is recognized in the literature, as evidenced by the increased integration of physiological measurements of exercise into study designs (Knutsen et al., 2006). This research further augments the literature by contributing to the quest for more rigorous measurement of exercise by helping to increase the accuracy and precision of the prescription of exercise intensity in breast cancer patients during chemotherapy treatment and survivors following treatment.

Although the sample was small, the inferential statistical analyses of the method averages within the groups indicated some significant differences. The descriptive statistics of the methods are equally valuable for drawing conclusions as well. The two different measures reported, achieved intensity, and accuracy (defined as the absolute value of the difference between the intended intensity of 60% VO2R and the achieved

intensity) both contribute meaningfully to the comparison of methods and the overall body of research.

Average achieved intensity

The results of the comparison of the average achieved intensities by each method within each group can be used to help establish a dose-response relationship of exercise intensity on specific outcomes. Often this type of research question requires a meta-analysis of several studies with similar research hypotheses. Example areas of research where the identification of a dose-response relationship would be beneficial in the breast cancer population include the effect of exercise intensity on $VO_{2peak,}$ parameters of cardiac function, and the immune system. In the group of studies included in the analysis, several different methods of exercise intensity prescription may have been used, and it cannot be assumed that different methods achieve the same intensity. This study provides a comparison of the intensities achieved by four common methods of exercise prescription. The small sample size of each group may preclude the use of this information from an actual quantification of the intensity, but the results can be used for general comparison. For example, in the survivor group, a common target population for exercise intervention research, it can be concluded that studies using the HRR, direct HR and MET equation methods to prescribe the same intensity would produce fairly similar results, whereas studies using the RPE method would achieve a significantly different result.

Range of achieved intensities

Not only is the average of achieved intensities by each method a useful measure for comparison purposes, but the range of achieved intensities by a method within each

group is also a valuable descriptive statistic provided by this study. It can be argued that the range of intensities achieved by a method is an important consideration in choosing an exercise intensity prescription method for studies involving both long-term exercise (i.e. intervention studies) and acute bouts of exercise.

Regardless of whether intensity is an independent variable in an exercise intervention study, standardizing the volume of exercise among study participants is crucial for estimating the effect of exercise on study outcomes. Of the components of exercise that contribute to the volume (frequency, duration and intensity), intensity is the hardest to control. If study participants were prescribed the same desired intensity of exercise with a prescription method that had a small range of achieved intensities, then it would be expected that most members in that group, assuming they meet their prescription target, would be exercising at a similar intensity. To demonstrate the effect of using a method with a large range, the direct HR method in the patient group can be taken as an example. The range of achieved intensities was 42 %VO_2R, with a maximum achieved intensity of 77%, and a minimum of 35%. Exercise intensities of 60-84 %VO_2R are reported to be more effective at increasing VO_{2max} than intensities of 40-59 %VO_2R (Swain, 2005). So it can be assumed that the group members would not receive the same training effect with this prescription method. VO_{2peak} is a common primary outcome of exercise intervention studies in breast cancer populations, and other outcomes are likely to be affected by this large amount of variability of exercise intensity as well.

Studies that intend to investigate the effect of an acute bout of exercise would also benefit from choosing a method with a smaller range of achieved intensities. For example, in cancer populations, there is recent interest in the effect of acute bouts of

exercise on various biomarkers. In studies of this nature it is critical that participants exercise at very similar intensities.

Average accuracy

The comparison of average accuracy of these methods provided by this study allows researchers and clinicians to make an informed decision on how to prescribe intensity in an exercise prescription. This information can be used to chose the method that is the most accurate, decide between methods that show similar accuracies based on availability of equipment or feasibility, or just to gain an appreciation of the accuracy of a method chosen for other reasons. In addition to the range, maximal and minimal achieved intensities, the average accuracy of each method is an important consideration in method choice in both exercise intervention studies and studies of acute bouts of exercise to ensure that all group members are exercising at similar intensities.

Clinical applications

The potential application of this study's research findings is clear, given the practicality of the research question and the method of assessment. Potential research applications of the study results have been outlined above, but there are potential applications in clinical practice as well. A survey of Canadian medical and radiation oncologists in 2002-2003 showed that the majority of oncologists agreed that exercise was a beneficial, important and safe intervention, and one-third reported recommending it to their patients in the past month (Jones et al., 2005). The dose-response relationship between VO_{2peak}, a measure of fitness, and all-cause mortality has long been established (Blair et al., 1995), and this variable is the strongest prognostic marker

of established cardiovascular disease (Keteyian et al., 2008). The importance of exercise to improve VO_{2peak} is evidenced by these statistics. Furthermore, the ACSM recently published a consensus statement indicating that there is overwhelming evidence from randomized control trials that exercise is safe, and that it is effective in improving aerobic fitness both during and after chemotherapy or radiation treatment for breast cancer (Schmitz et al., 2010). It is safe to hypothesize that with this recent unequivocal establishment of the safety of exercise and its effectiveness in improving a parameter as closely tied to health and mortality as VO_{2peak}, that the number of oncologists and other health care and exercise specialists prescribing exercise to their patients and clients with breast cancer will increase dramatically in the near future.

The methods of prescribing exercise compared in this study are feasible in clinical practice situations as well. For example, oncologists have the ability to order an exercise test that provides the objective physiological values necessary for the intensity prescription methods described in this study. Alternatively, although less effective, the prescription can be based on estimated or predicted values without the need for an exercise test. The value of including the role of a clinical exercise physiologist, someone trained in exercise testing, as a part of cancer rehabilitation programs is recognized (Lucia et al., 2003). In addition, the ACSM now offers a certification for a fitness professional trained to work with cancer populations following diagnosis, during and after treatment. The scope of practice of this certification includes fitness assessment and fitness recommendations.

The clinical routes of delivery of an exercise intensity prescription described here, although not comprehensive, are examples of other potential applications of the results of this study outside of exercise research. Knowledge of the accuracy of the

methods and the recommendations for method use for the two different breast cancer treatment timepoints are quite valuable in these situations as well.

Conclusions regarding thesis hypotheses

The hypotheses of this study were based on the compilation of literature regarding the different prescription methods in other populations, and the links between side effects of treatment and exercise response outcomes presented in the introductory chapter. These links were, for the most part speculative. This speculation was extended to hypothesize the impact of breast cancer treatment on the physiological relationships and metabolism constants on which the prescription methods are based to generate the study hypotheses.

H1: The HRR method will be the most accurate, and RPE the most inaccurate in the breast cancer patient group.

This hypothesis was supported.

H2: The intensity achieved by the RPE and MET equation methods will vary greatly from the intended exercise intensity for the breast cancer patient group.

This hypothesis was partially supported. The average achieved intensity for these two methods were the furthest from the intended intensity of 60% VO_2R, but the accuracy of the MET equation was quite high, and comparable to the HRR method, the most accurate for the group. The average achieved intensity of the RPE method did not deviate a great deal from the intended intensity, but it was the least accurate method of the four.

H3: The direct HR method will be the most accurate and RPE the most inaccurate in the breast cancer survivor group.

This hypothesis was partially supported. The second portion of the hypothesis regarding the inaccuracy of the RPE method was supported. The RPE method differed significantly in both intensity achieved and accuracy from all three other methods. The other three methods were all reasonably accurate and did not differ from one another statistically in achieved intensity or divergence, and had fairly similar variability. Therefore, all three methods could be considered accurate for prescribing exercise intensity in the survivor group.

H4: The intensity achieved by the RPE and MET equation methods will vary greatly from the intended exercise intensity for the breast cancer survivor group.

This hypothesis was partially supported. The average achieved intensity of the RPE method was the lowest of any group or method in the analysis. The average achieved intensity of the MET equation was nearly equal to the intended intensity.

H5: There will an interaction effect between group and method, meaning that each method will not show the same accuracy for each group.

This hypothesis was supported. There was a significant interaction effect.

H6: The HR methods (both HRR and direct HR) will be more accurate in the survivor and control groups than the patient group.

This hypothesis was partially supported. The contrast analysis supported that the average accuracy of the direct HR method was lower (higher divergence) in the patient group than that of the survivor and control groups combined. The HRR method accuracy was compared by contrast analysis between the patient and control groups

only. This contrast was not significant. A review of the descriptive statistics of the accuracy and achieved intensity indicate that the HRR method was the most accurate in the patient group, contrary to the hypothesis.

H7: The RPE method will not differ among the three groups.

This hypothesis was not supported. The accuracy of the RPE method for the survivor group was significantly different than that of the patient and control groups combined. The average intensity achieved by the RPE method within each group was also disparate between the groups.

H8: The recommended method will be HRR for the patient group and the direct HR method for the survivor group.

This hypothesis was supported. The HRR method was the recommended method for the patient group. For the survivor group, the direct HR, HRR, and MET equation were all recommended.

Strengths and limitations

Several of the study's strengths and limitations are presented in the discussion section of the research chapter. This discussion expands on some of those previously mentioned and presents some further points.

The inclusion of a control group in the study strengthens the study in two ways. First, as described in the research chapter, it provides some insight into intensity prescription in a healthy population. Although the sample size may be small, by merit of being the only study available to provide an empirical comparison of the accuracy of these methods in practice, the study results are useful. Second, it provides a basis for comparison. The differences among the methods in the cancer groups could not be

attributed to cancer or cancer treatment without knowledge of how the methods compare in healthy individuals. The outcome of the comparison of methods was not the same within the control group and the cancer groups. The methods based on objective physiological data actually varied less in the control group than both the cancer groups.

The inclusion of two groups representing different stages of cancer is another unique feature of this study. The two cancer groups allowed for comparison in prescription methods not just between each group and the healthy controls, but for a comparison between two different stages of treatment as well. As described in the introduction chapter, there is reason to believe that there are differences in physiology between the time periods of chemotherapy treatment where negative side effects tend to peak, and a later time following initial treatment where the short-term side effects may have worn off, but there is still potential for long-term side effects to develop. The three-group design proved to be a valuable design feature, as there was a significant interaction of group (representing treatment status) and method accuracy; and distinct recommendations for prescription method were generated for the two stages of treatment.

A further strength of the study design is that it was not imperative that the subjects reached a true VO_{2peak}, as is a common limitation in maximal exercise testing in clinical populations. The variable of concern was the accuracy of the prescription methods, and this was measured through their ability to elicit 60% of the *measured* VO_2R. However, in practice to accurately achieve the desired intensity level, a true VO_{2max} and/or HR_{max} is required, depending on the prescription method used. The feasibility of attaining a true maximum in cancer populations has not been explored.

A study limitation discussed in the research chapter is that the study design is limited to testing the accuracy of the methods in achieving just one intensity. There are a few other reasons, based on the study design, for choosing 60 %VO2R as the single intensity in the study. First, it is feasible, given the study procedures of testing all four methods in the same day, and the necessity to return to a resting state fairly quickly in between bouts. Second, it can be assumed that steady state oxygen consumption will be reached within three minutes at this moderate intensity, whereas higher intensities may take longer (Xu & Rhodes, 1999).

Future research directions

The intent of this study was to provide a comparison of four commonly used methods of exercise intensity prescription. There are several questions evoked by this study that would require future research involving in-depth analysis of each of the methods individually.

First, investigation of the accuracy of the MET equation method in achieving the intended intensity in the current study indirectly tested the applicability of the oxygen cost constants that are used in the ACSM metabolic equation for treadmill walking for the three groups in this study. Future research is needed to directly investigate whether there are differences in exercise metabolism among these groups. In the interim, the results of the present study do provide some insight. By using the measured value of VO_{2rest} in the equation instead of the constant value, the differences between the achieved intensity and intended intensity can then be attributed to variability in subject oxygen costs of walking from the constants used, assuming that steady state oxygen consumption had been reached by the last 5 minutes of the MET equation bout. As

discussed in the research chapter, the MET equation method was quite accurate in all three groups. Therefore it can be assumed that the oxygen consumption costs of treadmill walking were fairly accurate in both the breast cancer patient and survivor groups. There are other metabolic equations described by the ACSM to estimate energy cost of activities such as running, stepping, leg and arm cycling (Thompson et al., 2010). Considering the accuracy of the metabolic equation for walking in prescribing a target workload to achieve a desired exercise intensity, there is merit in investigating the accuracy of the other equations to provide other exercise mode options to the breast cancer population.

Our laboratory has previously investigated the change of the relationship between heart rate and oxygen consumption, and the impact of this change on the exercise intensity prescription derived from the direct HR method in breast cancer patients from pre to post-chemotherapy (Kirkham, Campbell, Jespersen, & McKenzie, 2009). This study included a sample of 30 women receiving varying chemotherapy protocols; and a few different patterns of changes in this relationship were recognized. A future research direction to build on the results of this previous study would be to investigate the changes in the heart rate and oxygen consumption relationship in a larger sample powered to analyze whether the patterns of change or extent of the change is related to specific chemotherapy protocols. This information would then aid in the prediction of accuracy in using the direct HR method during chemotherapy.

Another related study by our laboratory was the investigation of a pilot method of adjusting the target heart rate prescription derived by the direct HR method to adjust for changes in fitness after training in breast cancer survivors without repeated maximal testing (Kirkham et al., 2010). This investigation was fueled by the cost and feasibility of

frequent re-testing during an exercise intervention. This study piloted the method on a small sample of 11 subjects participating in an exercise intervention. The method shows promise for predicting the change in target heart rate necessary to continue to achieve a desired exercise intensity of 60% VO_2R from a simple submaximal exercise test using a treadmill and heart rate monitor only. The current study's results indicate that the MET equation method and the direct HR method are fairly accurate for short-term prescription in the survivor group. Future research investigating the validity of the aforementioned submaximal target heart rate prediction approach and/ or a similar approach to the prediction of changes in VO_{2peak} would increase the feasibility and potentially the accuracy of the MET equation and direct HR methods for long-term prescription.

Although the relationship between absolute heart rates and oxygen consumption was investigated in the aforementioned study, the relationship between relative (expressed as a percentage of reserve) heart rate and VO_2 has not been assessed for the breast cancer population at any treatment time point. Establishing the extent to which this relationship is true in breast cancer patients and survivors in future research could provide insight into the trend toward more accuracy of the HRR method in the patient group seen in the current study, and provide a firmer empirical basis for the current study's recommendations for use of the HRR method in the cancer groups.

There are other methods used to prescribe exercise intensity that do not use oxygen consumption as the gauge of intensity, including the use of the relationship between heart rate and blood lactate, percentage of peak power on a cycling ergometer and the percentage of maximal heart rate, as already discussed. The accuracy and

applicability of these methods in the breast cancer population should be investigated as alternatives to the methods compared in the current study.

Although the cross-sectional design of the study allowed for an important comparison of a group at the end of chemotherapy treatment and a group who have finished initial treatments, no information regarding temporal changes throughout treatment or recovery can be inferred. Future research is needed to determine the time course of physiological changes from diagnosis, throughout treatments, and recovery from treatment.

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Appendices

A: Study procedures

Measurement procedures of resting oxygen consumption and resting heart rate

Resting heart rate was measured on the second day of data collection immediately upon arrival. The subject sat quietly for 3-5 minutes or until heart rate stabilized. Next the subject was moved to sit next to the metabolic cart to measure resting oxygen consumption, again in a seated position. Continuous expired gas collection and analysis, and heart rate measurement were done for 6 to 10 minutes or until a steady resting oxygen consumption value was obtained for 2 continuous minutes. The resting oxygen consumption value used in the calculations was chosen as the average of the 2-minute block that showed both steady measurements throughout the 2 minutes, and the lowest average value after the initial 4 minutes of measurement. Heart rate was also continuously measured during this time period, and the value used in the calculations for resting heart rate was the lowest obtained during either period of measurement from the second day of data collection.

RPE instructions (Erhman et al., 2010)

"During the exercise test I want you to pay close attention to how hard you feel the exercise work rate is. This feeling should reflect your total amount of exertion and fatigue, combining all sensations and feelings of physical stress, effort and fatigue. Don't concern yourself with any one factor such as leg pain, shortness of breath or exercise intensity, but try to concentrate on your total, inner feeling of exertion. Try not to underestimate or overestimate your feelings of exertion; be as accurate as you can."

Borg scale rating of perceived exertion

6 – No exertion at all

7 – Extremely light

8 -

9 - Very light

10 -

11 - Light

12 -

13 - Somewhat hard

14 -

15 – Hard (heavy)

16 -

17 - Very hard

18 -

19 – Extremely Hard

20 – Maximal exertion

B: Ethics certificate of approval

The University of British Columbia
Office of Research Services
Clinical Research Ethics Board – Room 210, 828 West 10th Avenue, Vancouver, BC V5Z 1L8

ETHICS CERTIFICATE OF FULL BOARD APPROVAL

PRINCIPAL INVESTIGATOR:	INSTITUTION / DEPARTMENT:	UBC CREB NUMBER:
Donald C. McKenzie	UBC/Education/Human Kinetics	H09-03418

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:

Institution	Site
UBC	Vancouver (excludes UBC Hospital)

Other locations where the research will be conducted:
Allan McGavin Sports Medicine Clinic Exercise Physiology Lab

CO-INVESTIGATOR(S):
William Sheel
Amy Kirkham
Kristin Campbell

SPONSORING AGENCIES:
N/A

PROJECT TITLE:
Comparison of Aerobic Exercise Intensity Prescription Methods in Breast Cancer Patients and Survivors

THE CURRENT UBC CREB APPROVAL FOR THIS STUDY EXPIRES: January 26, 2011

The full UBC Clinical Research Ethics Board has reviewed the above described research project, including associated documentation noted below, and finds the research project acceptable on ethical grounds for research involving human subjects and hereby grants approval.

REB FULL BOARD MEETING REVIEW DATE: January 26, 2010	

DOCUMENTS INCLUDED IN THIS APPROVAL:			DATE DOCUMENTS APPROVED:
Document Name	**Version**	**Date**	
Protocol:			
proposal	Version 1	December 17, 2009	
Background	N/A	December 1, 2009	
Consent Forms:			
Consent form	2	February 10, 2010	
Advertisements:			
BC Recruitment poster	2	February 5, 2010	**February 12, 2010**
Control recruitment poster	2	February 5, 2010	
Questionnaire, Questionnaire Cover Letter, Tests:			
Subject eligibility checklist	2	February 10, 2010	
Other Documents:			
MSc Thesis Proposal report	N/A	December 15, 2009	

CERTIFICATION:
In respect of clinical trials:
1. The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations.
2. The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practices.
3. This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent form for the trial which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.

The documentation included for the above-named project has been reviewed by the UBC CREB, and the research study, as presented in the documentation, was found to be acceptable on ethical grounds for research involving human subjects and was approved by the UBC CREB.

Approval of the Clinical Research Ethics Board by one of:

Dr. Peter Loewen, Chair
Dr. James McCormack, Associate Chair

C: Individual subject data

Table 10: Subject characteristics: non-cancer medical history and current medications, menopause timing

		Non-cancer medical hx	List other	Non-cancer meds	List		
Group	**Subject #**	**Type (1=hypertension, 2=high cholesterol, 3=other, 4= none)**				**Time since last menstrual cycle (months)**	**Chemo-induced? (1=yes, 2=no)**
Patient	1	4		4		12	2
	3	4		4		3	1
	21	4		4		3	1
	23	4		4		5	1
	24	1,2		1		60	2
	25	4		4		3	1
	26	4		4		18	2
	28			4		60	2
	29	4		4		3	1
	30	4		4		3	1
Survivor	2	1		1	Novo-hydrazide, Cozaar	17	1
	4	4		4		96	2
	5	1		1	Adalat XL	26	1
	7	3	Pulmon-ary embolism	4		30	1
	12	4		4		36	2
	13	4		4		36	2
	14	4		4		20	1
	16	1,2		1,2	Vasotec, adalet, hydrochlorizide, lipitor	60	2
	17	4		3	Triptorelin	22	1
	18	4		4		24	1
Control	6	3	Osteo-porosis	3	Actinel (osteoporosis)	120	2
	8	2		2	Lipitor	60	2
	9	1,2,3	diabetes	1,2,3	Metformin, Lipitor, Cozaar	6	2
	10	4		4		12	2
	11	4		4		120	2
	15	3	Hyper-thyroidism	3	Hormone replacement, Synthroid (well-controlled)	48	2
	19	4		4		60	2
	20	2,3	Thyroid	2,3	Questor, (Thyroid-25 yrs)	24	2
	22	3	Osteo-arthritis	3	Acid reflux, allergies, joint pain	30	2
	27	3	Thyroid	3	synthroid (thyroid- 3 yrs)	3	2

Abbreviations: hx: history; meds: medications; chemo: chemotherapy; yrs: years

Table 11: Subject characteristics: physical activity in previous month and experience with treadmills, Borg scale and heart rate monitors

Group	Subject #	Frequency (#/week)	Intensity (1= easy, 2= moderate, 3= hard)	Duration (min)	Treadmill use in the past year (1=0x, 2=1-3x, 3=4-12x, 4=12+x)	Familiar with Borg scale (1=yes, 2=no)	Used heart rate monitor in past 5 years? (1=yes, 2=no)
Patient	1	3	2	50	4	1	1
	3	3	2	30	4	1	1
	21	3	2	30	4	1	1
	23	4	1	30	4	1	1
	24	3	2	30	4	1	1
	25	3	2	30	4	1	1
	26	3	2	30	4	1	1
	28	4	2	50	4	1	1
	29	4	2	50	4	1	1
	30	4	2	50	4	1	1
Survivor	2	5	2	60	1	1	1
	4	3	3	60	4	1	1
	5	4	2	50	4	1	1
	7	4.5	2	75	4	1	1
	12	5	2	60	1	1	1
	13	4	2	30	4	1	1
	14	3	2	40	4	1	1
	16	3	2	40	4	1	1
	17	3	2	45	4	1	1
	18	4	2	45	4	1	1
Control	6	9	2	45	3	1	1
	8	5	2	52	4	2	1
	9	4	2	35	3	2	1
	10	5	2	40	1	2	2
	11	3	2	60	1	2	2
	15	8	2	52	4	2	1
	19	5	2	60	2	1	1
	20	4	2	40	1	1	2
	22	3	2	60	4	2	2
	27	3.5	2	45	3	2	2

Table 12: Subject cancer and cancer surgery characteristics

Group	Subject #	Time since diagnosis (months)	Stage of cancer (1-3)	Side (1=left, 2=right, 3= both)	Time since surgery (months)	Surgery Type (1=lumpectomy, 2= mastectomy, 3=both)	# nodes removed	# nodes positive
Patient	1	7	3	2	6	1	1	0
	3	11	2.5	1	7	2	10	2
	21	9	undiagnosed	1	5	2	5	0
	23		2	3	9	2	5	0
	24	5	1	1	4	1	2	0
	25	7	2	1	6	1	10	3
	26	8	1	2	6	2	5	1
	28	7	2	2	6	1	20	5
	29	6	undiagnosed	2	5	1	2	1
	30	9	1	1	6	2	9	2
Survivor	2	18	3	2	17	3		
	4	28	3	2		1	22	22
	5	28	2	1	28	2	5	2
	7	33	undiagnosed	1	32	1	4	2
	12	22	3	1	20	2	21	2
	13	30	1	2	31	1	5	0
	14	24	3	1	23	1	1	0
	16	23	2	1	20	2	11	1
	17	26	3	2	25	2	3	2
	18	28	2	2	19	1,2	5	3

Table 13: Subject cancer treatment characteristics

Treatment type:		Chemotherapy			Radiation		Biological	Hormonal		
Group	Subject #	Type	Duration (weeks)	Time since last tx (weeks)	? (1= yes, 2= no)	# of tx's before Day 2	herceptin? (1=yes, 2=no)	? (1=yes 2=no)	Current ? (1=yes, 2=no)	Type
Patient	1	ACTTG	16	3	2		1	2	2	
	3	FECD	18	3	2		2	2	2	
	21	AC	12	4	2		1	2	2	
	23	ACTT	24	3	2		1	2	2	
	24	DC	12	4	1	3	2	2	2	
	25	FECD	18	4	2		2	2	2	
	26	DC	12	4	1	7	2	2	2	
	28	FECD	18	3	2	2	2	2	2	
	29	ACTG	16	3	2		2	2	2	
	30	FECD	18	4	2		2	2	2	
Survivor	2	FECD	18	54	1		2	1	1	Tamoxifen
	4	ACT	18	96	1		2	1	1	Arimidex
	5	FECD	18	95	1		2	1	1	Tamoxifen
	7	FECD	18	132	1		2	1	1	Letrazole
	12	ACTTG	16	68	1		1	1	1	Arimidex
	13	DTFEC	18	95	1		1	1	1	Tamoxifen
	14	ACTG	16	79	1		2	2	2	
	16	DC	12	74	1		2	1	1	Tamoxifen
	17	FECD	18	92	1		2	1	1	Exeme-stane
	18	FECD	18	90	1		2	1	1	Arimidex, Zolodex

Table 14: Subject characteristics: age, day 1 and day 2 data comparison of anthropometrics and resting values

				Day 1 of data collection					Day 2 of data collection				
Group	**Subject #**	**Age**	**Days b/w**	**Ht (m)**	**Wt (kg)**	**HR_{rest} (bpm)**	**SBP (mmHg)**	**DBP (mmHg)**	**Wt (kg)**	**BMI (kg/m^2)**	**HR_{rest} (bpm)**	**SBP (mmHg)**	**DBP (mmHg)**
Patient	1	48	8	1.68	70.4	77	110	80	70.9	25.1	77		
	3	50	3	1.54	53.7	80	104	70	52.9	22.3	81	117	75
	21	49	2	1.627	51.2	62	108	70	51.5	19.5	62	102	75
	23	43	8	1.739	69.5	79	112	82	68.3	22.6	70	122	80
	24	55	13	1.64	76.3	61	125	78	76.3	28.4	77	122	82
	25	44	2	1.655	59.5	64	110	70	60.5	22.1	61	110	62
	26	50	8	1.67	64.6	67	98	60	64	22.9	67	95	65
	28	49	3	1.758	78.4	55	118	76	78.5	25.4	54	115	75
	29	45	2	1.627	62.2	78	110	70	61.9	23.4	81	108	70
	30	44	3	1.637	71.2	74	90	70	71.7	26.8	60	92	70
Survivor	2	45	8	1.704	95.8	70	130	98	97.2	33.5	66	128	92
	4	58	5	1.552	68	51	130	85	68.6	28.5	56	120	92
	5	53	7	1.565	60.7	64	128	85	61	24.9	62	127	85
	7	54	8	1.76	99.6	84	128	76	100.1	32.3	68	105	85
	12	57	2	1.69	67.9	57	120	72	67.9	23.8	58	105	72
	13	53	2	1.758	73.1	66	120	72	73.4	23.7	58	119	72
	14	52	3	1.74	86.9	53	118	65	87.4	28.9	48	105	65
	16	59	4	1.708	104	76	142	88	105.4	36.1	75	138	75
	17	42	3	1.693	57.4	58	122	85	56.4	19.7	57	118	83
	18	47	9	1.62	68.1	65	105	65	68.5	26.1	63	108	65
Control	6	61	2	1.618	62.8	63	120	80	62.7	24.0	61	100	80
	8	53	9	1.6	61.1	75	95	65	60.3	23.6	73	95	70
	9	53	7	1.647	66	73	120	85	66.6	24.6	74	128	82
	10	46	7	1.638	58.3	53	115	75	58.9	22.0	53	110	75
	11	61	2	1.492	54.9	69	125	75	55.2	24.8	70	123	75
	15	56	7	1.553	56.1	58	132	75	57.1	23.7	55	118	72
	19	54	5	1.592	56.8	64	132	85	56.9	22.5	64	128	78
	20	52	2	1.547	103.8	87			103.7	43.3	70		
	22	56	7	1.66	62	64	120	85	63.2	22.9	66	125	82
	27	51	3	1.584	65.1	56	125	90	65.5	26.1	56	120	80

Abbreviations: days b/w: number of days between day 1 and day 2 of data collection; Ht: height; Wt: weight; HR_{rest}: resting heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index

Table 15: Subject maximal exercise test data part I

Group	Subject #	Test length (min)	Test speed (mph)	Mask or mouthpiece (1=mask, 2= mouthpiece)	Reason for test termination (1=dyspnea, 2=leg fatigue, 3=both, 4=other)	Final RPE	HR_{max} (bpm)	Gellish age-pred HR_{max}	2 min recovery HR	5 min recovery HR
Patient	1	13	4	1	1	20	188	175	115	110
	3	8.75	3	1	1	20	160	173	104	102
	21	12.25	3.5	1	1	20	173	174	109	101
	23	12	4	1	3	20	182	178	139	118
	24	11.25	3	1	1	19	149	170	103	96
	25	15	3.5	1	3	20	184	177	116	97
	26	8.5	3.5	1	1	19	161	173	94	95
	28	11.5	4	1	4	19	149	174	98	
	29	13.5	3.5	1	1	20	192	177	133	131
	30	13.5	3.5	1	1	20	173	177	111	102
Survivor	2	9.75	3.5	1	1	19	164	177	110	102
	4	12	3.3	2	1	18	174	168	111	103
	5	11.75	3.7	2	3	20	171	171	123	118
	7	12.75	3.2	2	4	17	177	171	147	112
	12	13	4	2	1	19	169	169	112	99
	13	13.5	3.9	2	1	17	180	171	121	110
	14	12	3.4	2	1	19	178	172	112	108
	16	9	3.5	2		18	164	167	118	109
	17	14.75	3.9	2	3	19.5	194	179	128	123
	18	16	3.3	2		20	170	175	109	102
Control	6	14.5	3.8	2	3	19	171	166	123	98
	8	14.75	3.5	2	1	20	181	171	122	114
	9	9.75	3.8	2		19	183	171	130	117
	10	12.75	3.7	2	2	20	181	176	126	104
	11	13	3.3	2		17	187	166	128	120
	15	14	3.3	2	4	20	175	169	108	95
	19	17.75	3.7	2		20	181	171	115	110
	20	12	2.6	2	4	19	181	172	129	118
	22	14.5	3.9	2	3	20	194	169	138	122
	27	14.75	3.8	2		20	170	173	107	95

Abbreviations: min: minutes; mph: miles per hour; RPE: rating of perceived exertion, HRmax: maximal heart rate; bpm: beats per minute; HR: heart rate

Table 16: Subject maximal exercise test data part II

Group	Subject #	Volitional exhaustion (1=yes, 2=no)	15-s plateau in VO_2 (1=yes, 2=no)	RER>1.1 (1=yes, 2=no)	HRmax +/- 5 bpm of Gellish age-pred HRmax (1=yes, 2=no)	Criteria count
Patient	1	1	1	1	1	4
	3	1	1	1	2	3
	21	1	1	1	1	4
	23	1	1	1	1	4
	24	1	1	1	2	3
	25	1	2	1	1	3
	26	1	2	1	2	2
	28	1	2	1	2	2
	29	1	2	1	1	3
	30	1	2	1	2	2
Survivor	2	1	1	1	2	3
	4	1	2	1	1	3
	5	1	2	1	1	3
	7	1	1	1	1	4
	12	1	1	1	1	4
	13	1	1	1	1	4
	14	1	2	1	1	3
	16	1	1	1	1	4
	17	1	1	1	1	4
	18	1	2	1	2	2
Control	6	1	1	1	1	4
	8	1	2	1	1	3
	9	1	2	1	1	3
	10	1	1	1	1	4
	11	1	1	1	1	4
	15	1	2	1	1	3
	19	1	2	2	1	2
	20	1	2	1	1	3
	22	1	1	1	1	4
	27	1	2	2	1	2

Abbreviations: S: seconds; VO_2: volume of oxygen consumption; RER: respiratory exchange ratio; HRmax: maximal heart rate; age-pred: age-predicted

Table 17: Subject oxygen consumption data

Group	Subject #	Relative VO_{2peak} (mL/kg/min)	Absolute VO_{2peak} (L/min)	VO_{2rest} (mL/kg/min)
Patient	1	33.7	2.37	2.7
	3	19.6	1.05	3.6
	21	28.6	1.46	1.8
	23	31.8	2.21	3.1
	24	20.9	1.59	3
	25	35.3	2.10	3.1
	26	23.6	1.52	1.7
	28	33.6	2.63	2.6
	29	31.7	1.97	2.2
	30	28.3	2.02	3
Survivor	2	25.1	2.41	2
	4	25.0	1.70	2.6
	5	29.9	1.82	3.2
	7	26.4	2.63	2.6
	12	35.8	2.43	3
	13	34.0	2.49	2.8
	14	25.2	2.19	2.7
	16	21.2	2.20	3.4
	17	39.6	2.27	3.4
	18	33.9	2.31	3.3
Control	6	37.3	2.34	3.5
	8	33.3	2.04	3.6
	9	32.4	2.14	3.8
	10	30.8	1.80	2.9
	11	26.4	1.45	3.6
	15	29.6	1.66	2.4
	19	41.3	2.34	3.7
	20	21.1	2.19	1.9
	22	37.2	2.31	3.2
	27	38.2	2.49	3.9

Table 18: Order of method randomization on day 2 of data collection

Group	Subject #	MET equation (#)	Direct HR (#)	RPE (#)	HRR (#)
Patient	1	4	1	2	3
	3	4	1	2	3
	21	2	4	3	1
	23	4	2	3	1
	24	3	2	1	4
	25	1	3	4	2
	26	1	3	4	2
	28	3	2	4	1
	29	4	2	1	3
	30	1	4	2	3
Survivor	2	2	3	4	1
	4	2	1	3	4
	5	1	3	2	4
	7	3	2	4	1
	12	4	2	1	3
	13	2	3	1	4
	14	1	4	2	3
	16	1	3	4	2
	17	2	1	4	3
	18	1	4	2	3
Control	6	4	2	1	3
	8	3	2	1	4
	9	1	4	3	2
	10	3	1	2	4
	11	1	2	3	4
	15	2	4	3	1
	19	2	3	1	4
	20	3	4	2	1
	22	4	3	1	2
	27	2	3	1	4

Table 19: Required data for prescription with each method

Group	Subject #	Target VO_2 (mL/kg/min)	MET equation - speed	MET equation - grade	Direct HR method - target HR	RPE method - target RPE	HRR method - target HR
Patient	1	21.3	3.5	5	147	12	144
	3	13.2	3	1	124	6	128
	21	17.9	3.5	4	127	9	129
	23	20.3	3.7	4	150	10	137
	24	13.7	2.9	2	105	10	120
	25	21.6	3.5	6	136	12	135
	26	14.8	3.2	3	118	11	123
	28	21.2	3.7	5	112	13	111
	29	19.9	3.5	5	147	11	148
	30	18.2	3.3	4	133	12	130
Survivor	**2**	15.9	3.3	3	123	7	125
	4	16.0	3.3	3	123	10	127
	5	19.2	3.5	4	129	11	128
	7	16.9	3.2	4	134	9	133
	12	22.7	3.9	5	127	11	125
	13	21.5	3.7	5	137	10	131
	14	16.2	3.3	3	122	10	126
	16	14.1	3.4	1	125	8	128
	17	25.1	3.9	6	148	12	139
	18	21.7	3.3	6	131	14	127
Control	**6**	23.8	3.5	6	129	13	127
	8	21.4	3.4	5	140	14	137
	9	21.0	3.4	5	138	13	139
	10	19.6	3.6	4	127	10	130
	11	17.3	3	4	141	13	140
	15	18.7	3.2	5	125	14	127
	19	26.3	3.7	7	134	13	134
	20	13.4	2.5	4	143	13	137
	22	23.6	3.7	6	133	12	143
	27	24.5	3.7	6	117	15	124

Table 20: Direct HR method data

Group	Subject #	VO_2R achieved (mL/kg/min)	$\%VO_2R$ achieved	Accuracy (ppts)	Avg HR
Patient	1	24.5	70%	10	147
	3	11.2	48%	12	125
	21	17.6	59%	1	128
	23	25.1	77%	17	153
	24	9.3	35%	25	107
	25	22.4	62%	2	140
	26	15.1	61%	1	120
	28	22.6	65%	5	113
	29	18.8	56%	4	148
	30	20.0	67%	7	134
Survivor	2	17.0	65%	5	124
	4	17.6	67%	7	125
	5	19.3	60%	0	130
	7	16.1	57%	3	135
	12	23.6	63%	3	129
	13	23.4	66%	6	139
	14	15.6	57%	3	123
	16	15.5	68%	8	124
	17	27.2	66%	6	149
	18	23.9	67%	7	132
Control	6	27.7	72%	12	128
	8	23.8	68%	8	139
	9	18.0	50%	10	139
	10	21.0	65%	5	130
	11	19.2	69%	9	141
	15	18.9	60%	0	126
	19	27.5	63%	3	134
	20	13.6	61%	1	144
	22	24.3	62%	2	134
	27	23.6	58%	2	116

Abbreviations: VO_2R: oxygen consumption reserve; ppts: percentage points; avg HR: average heart rate

Table 21: HRR method data

Group	Subject #	VO_2R achieved (mL/kg/min)	$\%VO_2R$ achieved	Accuracy (ppts)	Avg HR
Patient	1	20.9	59%	1	144
	3	13.8	63%	3	126
	21	18.0	60%	0	130
	23	21.5	64%	4	140
	24	12.8	55%	5	122
	25	22.2	62%	2	137
	26	16.3	67%	7	124
	28	21.3	60%	0	110
	29	18.4	55%	5	149
	30	19.6	66%	6	131
Survivor	2	17.3	66%	6	125
	4	15.8	59%	1	129
	5	20.7	65%	5	129
	7	16.6	59%	1	135
	12	22.4	59%	1	126
	13	21.8	61%	1	132
	14	18.6	71%	11	129
	16	16.3	72%	12	128
	17	23.2	55%	5	141
	18	22.9	64%	4	127
Control	6	26.7	69%	9	128
	8	22.8	65%	5	138
	9	20.5	58%	2	139
	10	22.1	69%	9	132
	11	18.7	66%	6	142
	15	21.2	69%	9	128
	19	27.5	63%	3	134
	20	12.4	55%	5	137
	22	27.1	70%	10	144
	27	26.6	66%	6	125

Abbreviations: VO_2R: oxygen consumption reserve; ppts: percentage points; avg HR: average heart rate

Table 22: MET equation method data

Group	Subject #	VO_2R achieved (mL/kg/min)	%VO_2R achieved	Accuracy (ppts)	Avg HR
Patient	1	20.0	56%	4	138
	3	13.1	59%	1	125
	21	17.4	58%	2	130
	23	20.5	61%	1	137
	24	12.9	55%	5	120
	25	21.9	61%	1	130
	26	12.2	48%	12	108
	28	18.4	51%	9	115
	29	18.1	54%	6	160
	30	17.2	56%	4	118
Survivor	2	16.3	62%	2	122
	4	16.5	62%	2	130
	5	19.6	61%	1	126
	7	16.5	58%	2	140
	12	23.3	62%	2	127
	13	19.7	54%	6	121
	14	15.2	55%	5	110
	16	14.9	65%	5	126
	17	26.0	62%	2	152
	18	19.2	52%	8	114
Control	6	23.8	60%	0	118
	8	20.8	58%	2	132
	9	20.8	60%	0	139
	10	18.7	57%	3	115
	11	16.1	55%	5	124
	15	18.5	59%	1	117
	19	26.5	61%	1	135
	20	13.4	60%	0	142
	22	24.4	62%	2	132
	27	24.0	59%	1	116

Abbreviations: VO_2R: oxygen consumption reserve; ppts: percentage points; avg HR: average heart rate

Table 23: RPE method data

Group	Subject #	VO_2R achieved (mL/kg/min)	$\%VO_2R$ achieved	Accuracy (ppts)	Avg HR
Patient	1	18.9	52%	8	132
	3	10.9	46%	14	118
	21	15.9	52%	8	122
	23	17.7	51%	9	135
	24	11.1	46%	14	116
	25	21.7	60%	0	135
	26	11.8	46%	14	112
	28	22.1	63%	3	122
	29	16.8	49%	11	133
	30	19.1	64%	4	128
Survivor	2	12.2	44%	16	99
	4	10.9	37%	23	106
	5	16.7	50%	10	113
	7	14.8	51%	9	132
	12	19.3	50%	10	108
	13	15.1	39%	21	104
	14	12.4	43%	17	99
	16	12.4	51%	9	112
	17	21.7	51%	9	134
	18	20.2	55%	5	117
Control	6	18.9	46%	14	101
	8	22.5	64%	4	130
	9	22.6	66%	6	148
	10	15.3	44%	16	102
	11	20.9	76%	16	152
	15	20.1	65%	5	124
	19	23.0	51%	9	125
	20	12.2	54%	6	134
	22	20.4	51%	9	121
	27	25.3	62%	2	120

Abbreviations: VO_2R: oxygen consumption reserve; ppts: percentage points; avg HR: average heart rate