COMPARISON OF METHODS FOR DETERMINING AEROBIC EXERICSE INTENSITY USING HEART RATE IN LEUKEMIA PATIENTS PRIOR TO INDUCTION CHEMOTHERAPY

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A thesis submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Masters of Arts in the Department of Exercise and Sport Science (Exercise Physiology).

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ABSTRACT

Christina Elizabeth Story: Comparing Aerobic Exercise Intensity Determination In Acute Leukemia Patients
(Under the direction of Claudio L. Battaglini)

PURPOSE: To compare different heart rate (HR) methods commonly used to determine aerobic exercise intensity in acute leukemia patients (ALP). METHODS: 14 ALP completed a VO_{2peak} test on a cycle ergometer with indirect calorimetry within 96 hours of admission at NC Cancer Hospital. The % of 220-age equation and HR reserve methods were compared to HR at $\%VO_{2peak}$ at 3 different exercise intensities; low (40%), moderate (60%) and high (75%). One-Way ANOVAs were used to compare different methods at different intensities. RESULTS: No significant differences were observed between 220-age and HR at $\%VO_{2peak}$ at moderate (100±8 and 113±24bpm, p=.122) and high intensity (125±10 and 123±25bpm, p=.994). At low intensity, all methods were significantly different. CONCLUSION: In ALP, neither % of 220-age or HR reserve should be used to prescribe aerobic exercise intensity, however, at moderate and high intensities, the 220-age equation produced similar values to HR derived from $\%VO_{2peak}$.

To my family, for their love and support of all of my endeavors – academic or otherwise.

To my mentor, Dr. Claudio Battaglini for his guidance,
mentorship and friendship during my time in Chapel Hill.

To the faculty, my friends and my classmates,
whose actions were invaluable over the last two years.

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CHAPTER ONE: INTRODUCTION

Background

Hematological cancers will make up a relatively small portion of new cancer diagnoses in the year 2015 with estimated total occurrences of 162,020 out of 1,658,320 new diagnoses of all cancers [American Cancer Society (ACS), 2015], and were expected to account for approximately 9.4% of cancer deaths overall in 2014 [Leukemia & Lymphoma Society (LLS), 2014]. Leukemia is the second-most common type of hematological cancer to occur with 54,270 new cases predicted this year (ACS, 2015). Out of all new leukemia diagnoses this year, Acute Myelogenous Leukemia (AML) will account for approximately 20,830 of those and over 10,000 deaths will be attributed to AML in 2015 (ACS, 2015). Acute Lymphocytic Leukemia (ALL) will account for approximately 6,250 new diagnoses this year and over 1,400 deaths will be attributed to ALL (ACS, 2015). The most common first treatment, induction chemotherapy, is successful in approximately 65% of AML patients and 80% of ALL patients, but the overall recovery and 5-year survival rate is significantly lower at less than 30% for AML patients and 40% for ALL patients (ACS, 2015).

The treatment plan for acute leukemia patients typically begins with induction chemotherapy for seven consecutive days, followed by three to four weeks of recovery time in the hospital. Two types of chemotherapy agents are used together with the goal of remission (which is defined as less than 5% of leukemia cancer cells in the bone

marrow) following induction therapy. After the recovery time, the next phase of treatment is called consolidation treatment, which is used to kill any remaining leukemia cells. This phase consists of three or more cycles of chemotherapy with a single agent that is given in the hospital for 5 days. The induction phase of seven continuous days of chemotherapy is intense for patients. The systemic physical assault of the body with these chemotherapy agents affects the majority of the body's physiological systems. Common side effects include nausea, diarrhea, fatigue, anemia, neutropenic fever and myelosuppression (Battaglini et al., 2011; Bryant et al., 2015). Adult acute leukemia is a rare diagnosis and treatment has fluctuating side-effects which are commonly observed in the majority of patients, including significant loss of body mass and lean body mass, reduced physical functional capacity, severe pain, and depressive symptoms and anxiety. All are major contributors to significant reduction in overall quality of life in this patient population (Battaglini et al., 2009; Alibhai et al., 2012; Bryant, et al., 2015).

Among treatment options such as chemotherapy and radiation in solid tumor cancers, exercise as an adjunct therapy has been shown to improve or decrease the decline of the outcomes (Schwitz, 2010). In the case of hematological cancers, there is little published research examining the potential benefits of exercise training, however the results of these initial trials have presented relatively successful outcomes in the alleviation of treatment-related symptoms in this cancer population. There is limited research yet to determine the most effective exercise prescription paradigm (i.e. mode, duration, intensity, frequency and timing within treatment) to maximize the potential exercise training benefits in patients with hematological cancers. Therefore it is paramount that additional studies are conducted to allow for the development of more

specific exercise plans for these patients with hematological malignancies (Battaglini et al., 2011).

Leukemia affects the ability of the body to produce red blood cells (RBC) that carry oxygen throughout the body to the tissues and organs. For instance, a decreased RBC count and therefore inadequate oxygenation may create problems with shortness of breath, increased heart rate, light-headedness; all factors influencing negatively the patients cardiopulmonary function thus reducing these patient's ability to exercise (National Library of Health, PubMed, 2013). However, in a previous study in patients with hematological cancers getting ready to undergo bone marrow transplantation, cardiopulmonary function has shown to be a strong predictor of post-transplant treatment complications and survival time (Wood et al., 2013).

Cardiopulmonary exercise testing (CPET) is the gold standard method of cardiopulmonary evaluation. It is a method that measures cardiopulmonary function objectively and it is often used for the determination of training thresholds in different populations including cancer patients (Jones et al., 2008). However, not every clinic or hospital has the equipment and personnel infrastructure to conduct CPET tests for the assessment of cardiopulmonary function and to use the results of a CPET to prescribe exercise intensity to their cancer patients. Examining other methods for the determination of exercise intensity that may produce accurate results when compared to the results of a CPET in a population so vulnerable to infections as AML patients may help clinicians to be able to prescribe exercise to their patients with less hassle and in a larger scale. Therefore, it is important to examine how well other methods of exercise intensity determination compare to the gold standard CPET.

Statement of Purpose

The purpose of this study was to compare the heart rate values computed from heart rate reserve method and the 220-age equation to heart rates obtained from a cardiopulmonary maximal exercise test for the determination of aerobic exercise intensity in newly diagnosed acute leukemia patients undergoing induction treatment.

Research Questions

RQ1: Is there a significant difference between heart rates derived from the heart rate reserve method when compared with heart rate values obtained from percent of the VO_{2peak} test at the intensities of 40%, 60% and 75%?

RQ2: Is there a significant difference between heart rates derived from the 220-age equation when compared with heart rate values obtained from percent of the VO_{2peak} test at the intensities of 40%, 60% and 75%?

Hypotheses:

H1: There will be an overestimation of exercise prescription intensity using the heart rate reserve method for the determination of aerobic exercise intensity at 40%, 60% and 75% when compared with heart rate values derived from the percent of VO_{2peak} test at 40%, 60% and 75%.

H2: There will be an overestimation of exercise prescription intensity using the 220-age maximal heart rate equation for the determination of aerobic exercise intensity at 40%, 60% and 75% when compared with heart rate values derived from the percent of VO_{2peak} test at 40%, 60% and 75%.

Definition of Terms:

Leukemia: A type of cancer that affects bone marrow and blood. The disease develops when cells formed in the bone marrow grow out of control. (LLS, 2014)

Acute Myeloid Leukemia (AML): A specific type of leukemia that affects several types of cells, which are not yet fully formed in the bone marrow (myeloid cells). AML's progression is considered fast (acute) and thus requires immediate intensive treatment for best survival outcomes. (LLS, 2014)

Acute Lymphocytic Leukemia (ALL): Also called Acute Lymphoid Leukemia, it is a specific type of leukemia that affects the bone marrow and blood. It is seen most often in children and adolescents, but over the past few decades an increasing number of adult cases have also been seen. (LLS, 2014)

Peak Oxygen Uptake (VO_{2peak}): Maximum rate of oxygen consumption as measured during incremental aerobic exercise and reflects aerobic physical fitness level. In this paper it will be referred to as a relative rate of milliliters of oxygen consumed per kilogram of body mass per minute (mL/(kg*min)). (Wikipedia, 2014)

Heart Rate (HR): The speed at which the heart beats, measured as the number of beats in a specific unit of time (usually beats per minute). A normal heart rate is between 60 and 100 beats per minute (bpm) at rest. HR can change according to the body's needs in terms of physical activity in order to absorb oxygen and carry it through the bloodstream. Some factors that can affect HR include stress, disease, sleep, drugs, illness, and exercise. (Wikipedia, 2014)

Heart Rate Reserve (HRR) Equation: (220–age–RHR)* %intensity + RHR. (Karvonen, 1957)

220-age Equation: (220-age) * % intensity (Robergs, 2002 and Fox, 1971)

Assumptions:

1. All of the participants followed pre-testing guidelines.
2. Participants answered honestly on all questions related to their history of cancer, lifestyle, health and medical issues.
3. On the peak oxygen consumption test, all participants gave maximum effort.

Limitations:

1. Sample was limited to adult acute leukemia patients currently undergoing treatment at UNC hospitals. Therefore, the outcomes of this study are unable to be generalized to other cancer types or other clinical populations.
2. Previous exercise history may have confounded outcomes.
3. Previous experience (or lack thereof) with exercise testing protocols may have influenced a patient's peak performance.

Delimitations:

1. All participants were adults, age 21 years and above.
2. All participants were recently diagnosed with acute leukemia and received treatment at UNC hospitals.
3. All participants underwent CPET test within 96 hours of admission.
4. All participants received the same type of treatment plan of 7+3 induction chemotherapy.

Significance of the Study:

The timely completion of acute leukemia treatment is a major factor in achieving remission and thus increasing the rate of survival. However, the severity of side effects

can decrease treatment plan compliance. The fluctuating side effects found in the leukemia population during treatment, including fatigue, can lead to decreased fitness capacity and difficulties performing the activities of daily living. This decreased functional capacity can lead to further fatigue and reduced ability to tolerate and complete treatment as planned. Over 90% of AML patients report fatigue as one of their most distressing symptoms (Alibhai et al., 2012). Bryant et al (2015) proposes that greater reductions in cancer-related fatigue are found in patients using moderate to high intensity exercise interventions. Battaglini's study in 2009 suggests that the continual negative cycle of decreased functional capacity and fatigue can be broken and quality of life can be maintained during treatment using exercise intervention. An exercise intervention during treatment may also reduce the length of hospital stays thus decreasing time to remission status.

However, there is no standardization of exercise protocols and therefore mixed degrees of success have been achieved regarding the desired outcome variables. The restrictions of using fatigued, immune-compromised acute leukemia patients, who are required to stay in their room for the duration of induction treatment, creates some difficulties as which may not be encountered during standard exercise protocols among cancer survivors and other clinical populations. Such difficulties include access to exercise equipment, exercise test availability and suitability as well as the infection risk to the patients.

At this time, the recommendations for exercise are generalized for the cancer population and are the same as the Physical Activity Guidelines for Americans, including the recommendation of 150 minutes of moderate intensity exercise per week (Schmitz et

al, 2010). Heart rate is used in most exercise intervention research programs because of its practicality in both supervised and unsupervised settings. It is a relatively easy and inexpensive way to monitor exercise intensity for either an administrator or the patient themselves. This leads to the simple question of which HR prediction method is more accurate to prescribe intensity of exercise.

Both the Heart Rate Reserve (HRR) method and the 220-age equation multiply a percentage of intensity by the predicted maximum to find a HR value equivalent to the chosen intensity level. For these equations, HR is assumed to increase in a linear fashion as intensity of exercise increases, and will move toward the maximum predicted value of 220-age beats per minute (bpm) (Robergs, 2002). A possible way to validate the use of the heart rate reserve and 220-age HR values at particular intensities is to perform a cardiopulmonary maximal exercise test (CPET) with HR values taken at small, regular intervals throughout the test. From the CPET test, a HR value at a certain intensity can be computed and compared to the predicted HR values given by the equations at the same level of intensity.

Currently the Heart Rate Reserve (HRR) method and the 220-age equation are two of the most commonly used methods to calculate HR values for varying levels of aerobic exercise intensity in different populations. Investigating several exercise intensities in this study will enable us to determine if either equation can be used to accurately to prescribe exercise in this sample of cancer patients. This is significant, since the use of the heart rate reserve and 220-age equation is easy to use and could assist exercise physiologists in the training of their patients with greater accuracy and without performing a CPET. Improving our understanding of the use of HR values for prescribing

exercise in acute leukemia patients will allow for clinicians to make a more informed decision as to which methods more closely correlate to the HR value derived from a CPET, which is considered the gold standard method for derivation of exercise intensity.

CHAPTER TWO: LITERATURE REVIEW

Overview

For the purpose of organization, this literature review will be divided into four sections. Facts and statistics on cancer and leukemia will be reviewed in the first section. Acute leukemia treatments and common side effects will be discussed in the second section. Studies on exercise and leukemia will be described in the third section. Lastly, section 4 reviews the prescription of aerobic exercise using heart rate.

Section 1: Statistics on Cancer and Leukemia

In the year 2015, over 1.6 million new cancer diagnoses are predicted, with more than 500,000 deaths from all cancer types. Over 50,000 of those new diagnoses this year will be new leukemia cases, and approximately 24,000 deaths will be attributed to leukemia as well (ACS, 2015). Those deaths from leukemia will account for 4.9% of all cancer deaths this year. Acute Myeloid Leukemia (AML) is the most common type of acute leukemia in adults and the second most common type of leukemia overall. Over 20,000 new diagnoses are predicted in 2015 with over 1,600 of those occurring in North Carolina alone. In regards to Acute Lymphocytic Leukemia (ALL), over 6,000 new cases will be diagnosed in 2015 (ACS, 2015).

Leukemia is a cancer that affects the bone marrow and the blood. Disease occurs when the cell growth rate in the bone marrow is exponentially increased and out of control (ACS, 2014). The type of leukemia is classified by the rate of cell growth (acute

or fast-growing versus chronic or slower growth) as well as the type of cell affected. In AML, the bone marrow is manufacturing abnormal immature cells of several types, excluding certain white blood cells (lymphocytes). Once a marrow cell becomes leukemic, it multiplies into over 10 billion cells that do not function normally and may prevent the production of other cells (LLS, 2014). Unlike solid tumor cancers, the specific sub-type of cell that it affects, not stage numbers I-IV classify acute leukemia.

AML typically has a greater incidence rate as age increases, with an average age at diagnosis of 66 years. Overall, the lifetime chance of diagnosis is 1 in 227 for men and 1 in 278 for women. 60-70% of AML patients achieve remission after the first phase of treatment, but only 25% are truly cured and survive more than 3 years giving AML the lowest long-term survival rate among the 4 different types of leukemia (LLS, 2014).

Section 2: Acute Leukemia Treatments and Common Side Effects

The most common and effective first-line treatment for acute leukemia diagnoses is intense chemotherapy in two distinct stages, induction therapy and consolidation therapy. Induction chemotherapy, the first phase, involves an intensive treatment with multiple chemotherapy drugs given in concert. An anti-tumor drug such as Antracycline and a drug from the anti-metabolite group such as Cytarabine are often given in a structure called 7+3 intensive treatment. This means that for 7 consecutive days, the anti-metabolite drug is dosed intravenously and for the first 3 of those days, the anti-tumor drug is also given. The goal of this very intensive treatment is to get rid of the leukemic cells, which are called leukemic blasts (LLS, AML Education Booklet).

Following the seven days of treatment, the patient will take 4 to 6 weeks to recover in the hospital as their immune system has been entirely wiped out by the chemotherapy

treatment. If the first round of treatment does not lead to remission, then a second round of induction chemotherapy will be started as soon as is tolerable by the patient. If the treatment has been successful, less than 5% of the bone marrow cells will be leukemic and the patient will progress to the next stage of chemotherapy treatment.

Consolidation chemotherapy is the next stage of treatment following the induction phase. The goal of this additional chemotherapy is to remain in remission and kill the remaining cancerous cells to hopefully prevent a recurrence or relapse. The length of stay and treatment plan varies but generally involves several single-drug treatments spread throughout the week with time spent alternately in the hospital and at home. This stage of treatment may also be paired with stem cell transplantation in certain cases to replace patient's bone marrow with healthy non-cancerous cells. (LLS, AML Education Booklet)

Side effects from chemotherapy vary in number and intensity across patients and treatment plans, but the most common ones in acute leukemia patients will be discussed here. The most serious effect of the chemotherapy is the low blood counts that result from the cell destruction of both cancerous and healthy cells in the bone marrow and blood. Red blood cells (RBC), white blood cells (WBC) and platelets will all be lowered by induction chemotherapy treatment. Transfusions of RBC and platelets are sometimes given to raise blood levels during the induction phase. The most dangerous effect of these low blood counts, especially WBC, will be the increased chance of infection. Infections can cause the patient to become septic in just a few hours due to their reduced immune system, so treatment with antibiotics must be started immediately to improve chances of recovery.

Other physical side effects of chemotherapy are similar to those seen in other cancers such as mouth ulcers, diarrhea, hair loss, rash, nausea and vomiting. Increases in anxiety, depression and fatigue are also often observed, with fatigue being reported as distressing by over 90% of AML patients (Alibhai et al, 2012).

Section 3: Exercise and Leukemia

Exercises as an adjunct therapy has been proven successful and efficacious in several other types of cancer in improving fatigue, quality of life and functionality (Schmitz, 2010), and exercise research with hematological cancer populations such as leukemia have also shown positive benefits. However, the limited number of studies regarding exercise in the acute leukemia population implies that the most effective methods and plans of exercise prescription for this population may not have yet been found or studied. The research studies that will be reviewed are Chang et al (2008), Battaglini et al (2009), Klepin et al (2011), and Alibhai et al (2012).

Chang et al (2008) was the first study in this population, and the only randomized controlled clinical trial. This study measured the outcomes of fatigue, 12-minute walking distance, symptom distress and mood disturbance both at baseline and at the completion of the 3-week program. The intervention group completed a walking exercise program consisting of 12 minutes of accompanied walking in the hospital hallway 5 days per week at an intensity of resting heart rate (RHR) plus 30 beats per minute (bpm) monitored via portable HR monitor. The study found statistically significant improvement in the 12 minute walking distance, as well as non-significant improvement in fatigue intensity, anxiety and depression (mood disturbance).

Battaglini et al (2009) completed assessments of fatigue, depression, quality of life (QOL), body composition, cardiovascular (CV) endurance, and dynamic muscular endurance at baseline and at study completion (approximately 6 weeks from start of treatment). Each patient was prescribed an individualized plan of exercise 3-4 times per week with at least 12 hours between sessions. Each session was divided into 2 bouts (AM and PM) and lasted for no longer than 30 minutes each. Each bout consisted of 3-5 minutes (min) of light stretching, 5-10min of cycling or treadmill walking, 5-15min of resistance training, and 5-10min of core exercises. Intensity for aerobic exercise was determined using heart rate reserve (HRR) of 40-50% and RPE on the CR10 modified Borg scale. RPE was monitored and never exceeded 5 on the 1-10 scale. This study found statistically significant improvements in CV endurance, fatigue and depression.

The study by Klepin et al in 2011 looked at the variables of lower-extremity physical functioning, grip strength dynamometry, health-related QOL, and additional measures such as depression and distress. The exercise intervention in this study consisted of group sessions offered 3-4 times per week for 4 weeks and included 5-15min of walking, 15min of tailored stretching and resistance training with resistance bands, and finishing with an additional 5-15min of walking. The prescribed intensity for the walking portion was "light" and participants reported an average RPE of 10.5 on the Borg scale of 6-20. Outcomes included a clinically significant improvement in the lower-extremity physical functioning test, as well as statistically significant improvement in health-related QOL and depression.

The most recently published study by Alibhai et al in 2012 studied the outcome measures of aerobic fitness (modified Bruce protocol, calculating $VO_{2\ peak}$ using ACSM

walking equation), 6-minute walk test, grip strength via dynamometer, lower body function via chair stand test, QOL, fatigue, depression and anxiety. Based on the results of the tests, each patient was approached with an individualized exercise prescription of 4-5 sessions per week for 30-45min per session and a total of 4-6 weeks. Each session included minimum of 10 (maximum of 40min) of aerobic training, 10min (up to 25min) of resistance training, and 5-10min of flexibility training. The intensity for the aerobic training was light to moderate and monitored via RPE scale of 3-6 (0-10 scale). Aerobic exercise progression was achieved by increasing duration first, then by increasing intensity. Improvements were clinically significant for fatigue, statistically significant for 6-minute walk test and anxiety, and non-significant improvements were seen in $VO_{2\ peak}$ and chair stand test.

Overall, each of these four studies prescribed varied exercise intervention during induction chemotherapy treatments and all showed statistically or clinically significant improvements in at least one variable of study. Those improvements were seen in both quality of life measures, including anxiety, depression, and fatigue, as well as physical functioning and fitness measures such as 6-minute walk test, lower extremity function and cardiovascular endurance. The methods of exercise prescription were varied in their mode, intensity and duration thus more research is needed to determine the most effective method of prescribing exercise so one can optimize the benefits of exercise in this cancer population. The findings of research conducted today on the use of exercise as an intervention used to alleviate treatment-related symptoms support the use of exercise in acute leukemia patients undergoing induction chemotherapy.

Section 4: Prescriptions of Aerobic Exercise using Heart Rate

Several studies have looked at the prescription of aerobic exercise intensity in other cancer populations such as breast cancer. One such study is by Evans et al (2009), which looked at HR, RPE and blood lactate (BL) values of breast cancer survivors as compared to healthy controls after aerobic exercise bouts. Participants were taken through a short 9-minute bout at each of three intensities (40%, 60% and 70% of calculated $VO_{2\ peak}$); all variables were measured at the end of each bout. No statistical differences between the groups were found for HR or RPE at any intensity level. The cancer group was significantly lower in BL values at 70% intensity, but not at 40% or 60%.

A second study by Kirkham et al in 2013 compared 4 methods of prescribing exercise intensity within and between 3 groups (recent breast cancer treatment completion, breast cancer survivors, and healthy controls) at 60% intensity. The four methods of intensity prescription include ACSM metabolic equation for treadmill walking, direct measured relationship between HR and VO_2 (HR_{direct}), the Heart Rate Reserve (HRR) method, and the RPE method. Each method's calculation of 60% was compared to 60% of VO_2 reserve (= $VO_{2\ peak} - VO_{2\ rest}$) for each participant. The study concluded that different methods of prescription were more accurate for certain groups than others. For breast cancer patients and survivors, HRR method and the ACSM metabolic equation were found to be most accurate. The four methods varied in accuracy and did not all achieve equivalent intensity prescription within each group.

These studies both present interesting and relevant research in regards to the comparison of methods of the prescription of exercise intensity. Kirkham et al in

particular shows the discrepancy between the methods, while also describing the most accurate for the clinical population in question. Unfortunately, both of these studies use breast cancer patients who have already completed treatment and are categorically different in their type of cancer and stage of cancer treatment, which allows for no comparison to be made to acute leukemia patients proposed in this study.

The exercise research in AML patients above has focused on feasibility and light to moderate prescription of exercise based on RPE or HRR. However, no analysis of the accuracy of these methods has been completed in this population as they undergo intensive chemotherapy treatment and such analysis is needed to ensure that the population is receiving the most accurate and beneficial exercise prescription possible.

CHAPTER THREE: METHODOLOGY

Participants

Acute Leukemia patients newly diagnosed with acute myelogenous or acute lymphocytic leukemia, ages 21 years or greater, admitted to begin induction chemotherapy with an expected hospital stay of 3-4 weeks, and enrolled to participate in the EQUAL (Exercise and Quality of Life in Leukemia/Lymphoma Patients) phase II trial, were included in this study. Patients were made aware of the EQUAL phase II study by their oncologists, and after approval by the oncologist to participate in the study, patients were contacted by a research team member where patients received further information regarding the study protocol. After the patients agreed to participate in the study, patients were asked to sign an informed consent form approved by the Lineberger Comprehensive Cancer Center Protocol Review Committee (LCCC PRC) and the University of North Carolina Institutional Review Board (IRB). All initial study assessments were performed within 96 hours of hospital admission.

The inclusion criteria to enroll in the EQUAL phase II trial included: being newly diagnosed with acute leukemia (AML or ALL) based on pathology report, physician approval, age of 21 years or older, ability to speak and understand English. The exclusion criteria were based on the risks of any normal exercise program, and included: cardiovascular disease; acute or chronic respiratory disease; acute or chronic bone, muscle or joint abnormalities; altered mental state, dementia, or any other psychological

condition that would prevent understanding of informed consent; another active malignancy; active bleeding, acute thrombosis, ischemia, hemodynamic instability, or uncontrolled pain. These criteria were determined by reviewing the patient's medical history and permission of the patient's physician.

A medical history questionnaire was completed to determine the patient's medical and cancer history including treatment, level of physical activity, age, race and gender. Prior to enrollment, all possible patient participants underwent a complete physical evaluation conducted by the physicians who were part of the research team. The patients underwent an EKG, as well as an echocardiogram (ECHO) or MUGA test (Multigated Acquisition Scan) for the assessment of cardiovascular function. The MUGA test, also called equilibrium radionuclide angiogram or blood pool scan, evaluates the pumping function of the ventricles (ejection fraction).

Instrumentation

For this study, only the data collected during the initial cardiopulmonary test were used from the patients enrolled in the EQUAL phase II trial. All tests were performed on a cycle ergometer (Monark 874E, Goteborg, Sweden) at the NC Cancer Hospital, Hematology Oncology Unit. To determine oxygen uptake, expired gases were measured via a portable metabolic gas analysis system (Cosmed Portable K4b2, Rome, Italy). Blood pressure (BP) was monitored via auscultation using a sphygmomanometer (American Diagnostics Corporation, Hauppage, NY) and a Littman Stethoscope (3M, St. Paul, MN). Heart rate (HR) values were be collected using a Polar telemetry system (Polar Electro Inc., Lake Success, NY) every 10 seconds during the CPET test. The Borg Rate of Perceived Exertion (RPE) Scale (6-20) was used to monitor rate of perceived

exertion (RPE) (ACSM, 2013) in the patient at the end of each stage of the CPET and at the end of the test.

Research Design Overview

This study was a retrospective study using data collected from the EQUAL phase II trial (IRB # 13-1082), a randomized clinical pilot trial that is being conducted by Dr. Ashley Leak Bryant and Dr. Claudio L. Battaglini. The study was a one-arm study only using data collected from the CPET test conducted at the beginning of the trial.

General Procedures

Informed Consent and Baseline Data

After eligibility was determined and prior to study enrollment, all patients were given a complete explanation of the EQUAL phase II trial and were allowed time to look over all consent forms. After the patient was provided with the information and the investigator was confident that participation implications were understood, patients were asked to sign the approved informed consent form. After the informed consent form was signed, patients were scheduled to participate in the initial battery of assessments. All patients underwent the exact same testing protocol at baseline and at the completion of the EQUAL study phase II protocol which included physical, functional, and psychosocial measures. For this study, only data from the CPET test conducted at baseline were used.

For the EQUAL phase II trial, patients were randomized into the intervention or to a standard of care group. For the current study, data from all patients during the baseline CPET were used regardless of group placement for the EQUAL phase II trial. Prior to testing, patients were asked to follow American College of Sports Medicine

(ACSM) pre-testing guidelines (ACSM, 2013). Medical personnel part of the research team collected demographic data (age, gender, language preference, disabilities, etc.) and, on the day of the initial assessment, resting vital measurements including resting heart rate (RHR), BP, temperature and oxygen saturation (SpO_2%).

Cardiopulmonary Exercise Test (CPET)

A cardiopulmonary exercise test (CPET) using standard procedures was used to determine $VO_{2\ peak}$. A member of the research team familiarized patients with the cycle protocol. The equipment was adjusted to fit the patient to achieve approximately 120° of extension of the lower leg when the pedal was closest to the ground. Patients were also fitted for a mask that was used to collect expiratory gases for the VO_2 analysis.

Prior to beginning the cycling protocol, patients sat in a resting state in order to collect two minutes of resting metabolic data via expiratory gas analysis while seated on the bike. Patients then cycled for 2 minutes at a resistance of 0 Watts as a warm-up, and the test started immediately following the warm-up period.

The initial workload used was 25 Watts, and workload increments were determined by medical history and patient's metabolic response during the first two minutes of cycling during the warm up. Workload increased 5-20 Watts, depending on the physical state of the patient, per minute until patients reached volitional fatigue.

Test termination criteria were: volitional fatigue, achievement of a respiratory exchange ratio (RER) of greater than 1.10, or limitation by symptoms. Symptoms that ended a test immediately included chest pain, ischemic changes on EKG, arterial oxygen

saturation of 85% or less, blood pressure response considered abnormal to exercise conditions, dizziness or nausea.

During the test HR, RPE, BP and VO_2 were recorded. HR values were recorded every 10 seconds and RPE was recorded at the end of every minute before increasing to the next workload. The average of the 3 highest values of oxygen uptake during the last minute of the test were used to determine $VO_{2\ peak}$. Following the test, patients were allowed to rest and cool down by pedaling at low workload of 10 Watts at a cadence of their choice until HR returned to under 120bpm. This protocol has been used previously in cancer populations and has been shown to be appropriate for $VO_{2\ peak}$ determination (Wood et al, 2013).

VO_{2peak} and HR data

The HR data were collected during the CPET in intervals of 10 seconds. Using the peak VO_2 obtained during the CPET (the averaging of the 3 highest values during the last minute of the test prior to termination), percentages of VO_{2peak} at 40% (low intensity), 60% (moderate intensity), and 75% (high intensity) were calculated. From the printout results of the CPET, values corresponding to the percentages of the three different intensities (low, moderate, and high) were determined using 30 seconds of raw VO_2 data and were averaged to determine the percentages at 40, 60 or 75% of VO_{2peak}). Then, the corresponding heart rates that were collected at the same 30 second interval used for the determination of the percent VO_{2peak} intensity were averaged to determine the corresponding HR value. The HRs determined from the VO_{2peak} percentage test were used for comparisons to HRs derived from the HRR and 220-age methods of aerobic

intensity determination at the three different exercise intensities. Figure 1.0 is a graphical representation of how HRs were determined from VO_{2peak} at different percentages.

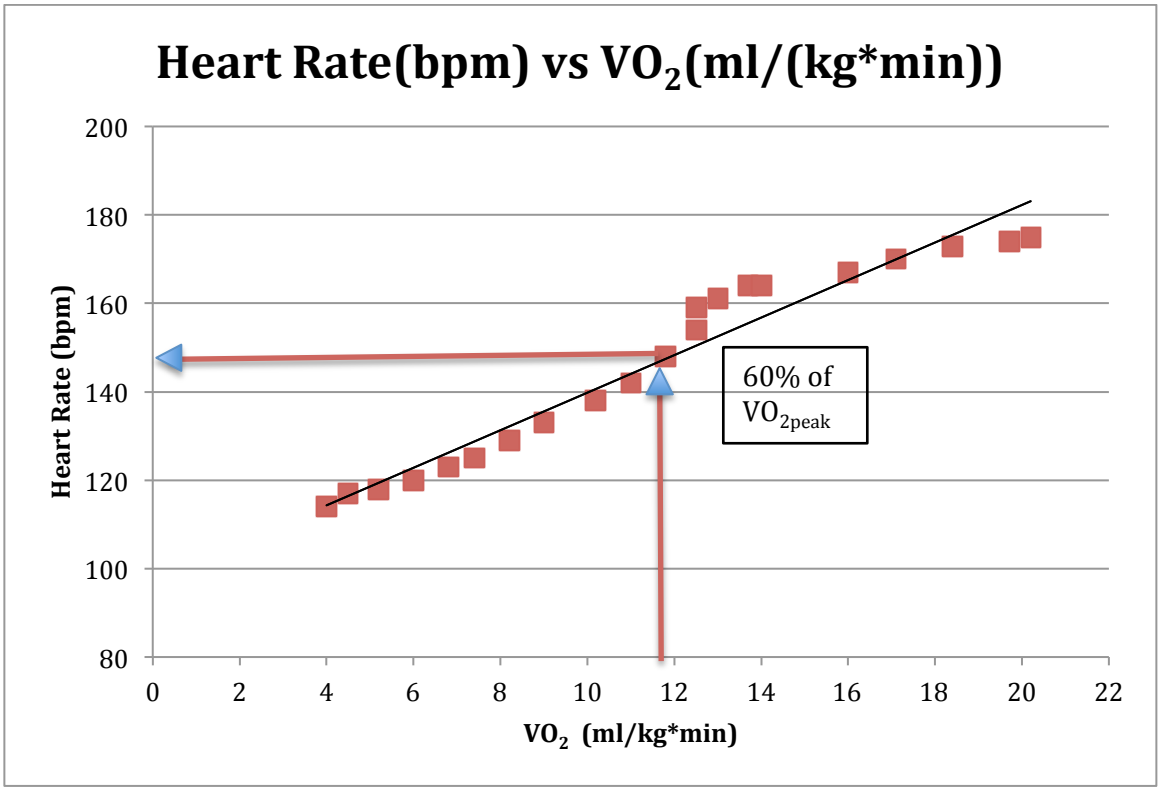


Figure 1.0: HR(bpm) vs. VO_2(ml/(kg*min)). This example data is from the VO_{2peak} test of one bone marrow transplant patient who completed the same testing procedure used in this study.

To obtain two different calculated values for each intensity level, which were compared to the HR values obtained from the VO_2 test, the Heart Rate Reserve (HRR) method ((HR_{max}–RHR)* %intensity + RHR) and the 220-age HR method ((220-age) * % intensity) were used at the same three exercise intensities (40%, 60% and 75%). The calculation for 40% was as follows: 40% of HRR (bpm)= (220-age-RHR)*0.40 + RHR. A similar process was completed for the 220-age equation, excluding the use of RHR: HR @40% (bpm) = (220-age)*0.40. Thus each participant has three HR values (1 actual

(from the VO2peak test), 2 calculated (from the HHR and 220-age methods)) for each of the three intensities that were investigated.

Statistical Analysis

This is a retrospective study using data from the CPET conducted as part of the EQUAL phase II trial.

On average, the NC Cancer Hospital receives 50-60 newly diagnosed acute leukemia patients per year. The EQUAL study aims to enroll 30 patients over 2 years. Using G-power analysis program, a sample size of 15 patients has 70% power to detect an effect size of 0.60. This analysis was completed using the parameters of a mean difference of 6bpm, and a standard deviation of the difference of 10bpm.

Descriptive statistics of means and standard deviations were calculated for age, height, weight, resting heart rate, and maximum HR achieved during the test (True Max). An alpha level was set *a priori* at .05. All statistical analysis was performed using SPSS software version 22.0 for Mac OS (IBM Solutions, Durham, NC).

The three models of aerobic exercise intensity determination (HR intensity derived from the CPET Test, HR intensity derived from the HRR method, and HR intensity derived from the 220-age equation) computed at three different exercise intensities (40%-Low Intensity, 60%-Moderate Intensity, and 75%-High Intensity) were compared using One-Way within subjects ANOVA models. If the ANOVA model turned out to be significant, post hoc analyses using the Sidak method were used to identify where significant differences in HR between methods occurred.

CHAPTER FOUR: RESULTS

The purpose of this study was to compare the heart rate values computed from heart rate reserve method and the 220-age equation to heart rates obtained from a cardiopulmonary maximal exercise test for the determination of aerobic exercise intensity in acute leukemia patients undergoing induction treatment. Fourteen adult acute leukemia patients were tested to compare obtained heart rates from the cardiopulmonary maximal test to the calculated heart rates from the heart rate reserve method and 220-age equation. Subject characteristics are presented in Table 1.0.

Table 1.0: Subject Characteristics

Subject	Age	Weight (kg)	Height (cm)	Resting Heart Rate (bpm)
1	34	69.8	155	95
2	58	90.3	187.9	59
3	64	86.5	165	98
4	40	128	198.1	81
5	57	102.2	184.2	77
6	43	95.5	182	86
7	28	116.6	164	93
8	67	97.7	188	67
9	67	47.5	153	69
10	57	74.1	160	57
11	64	74.1	163	57
12	69	93	187	89
13	60	94.8	182.5	60
14	39	60.6	188	75
Mean ± SD	53 ± 14	87.9 ± 21.4	175.6 ± 14.8	76 ± 15
Min – Max	28 – 69	47.5 – 128.0	153.0 – 198.1	57 – 98
Range	41	80.5	45.1	41

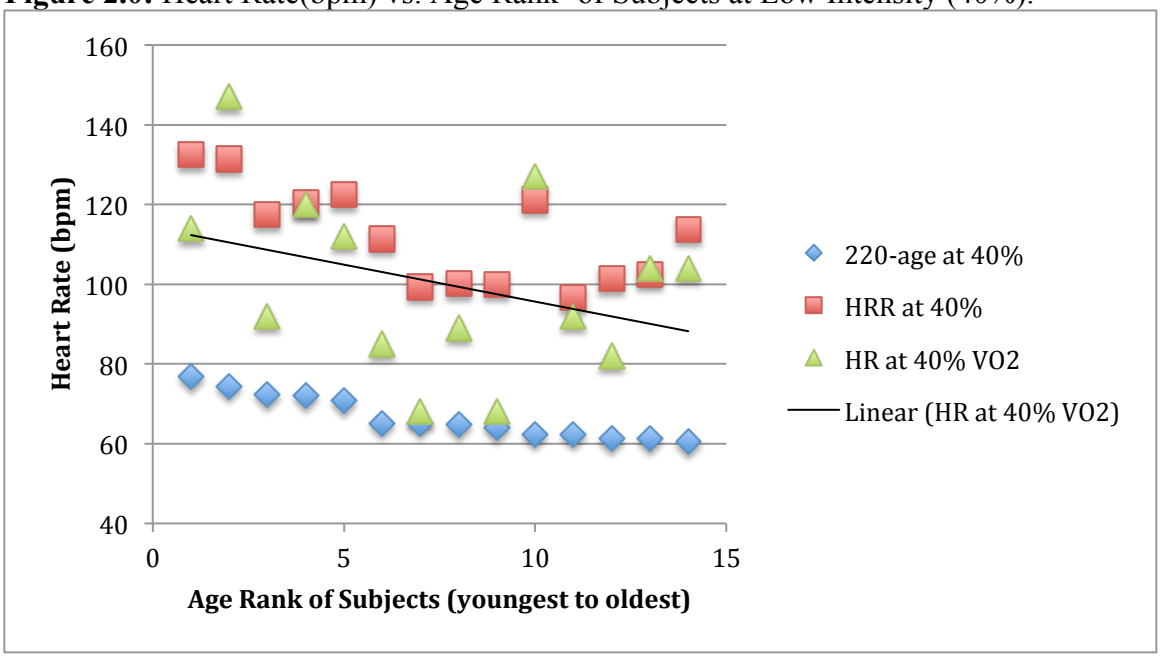
Descriptive statistics on the results of calculations of HR at % VO_{2peak} test and HR calculations using the heart rate reserve (HRR) and 220-age equations at low (40%), moderate (60%) and high (75%) intensities are presented in Tables 2.0, 3.0, and 4.0.

Table 2.0: Calculated HRs for Low Intensity (40%)

Subject	HRR (bpm)	220-age (bpm)	HR at % VO_{2peak} (bpm)	% True Max (bpm)
1	131	74	147	51
2	100	65	89	51
3	121	62	127	62
4	121	72	120	62
5	111	65	85	48
6	122	71	112	68
7	133	77	114	66
8	101	61	82	50
9	103	61	104	49
10	99	65	68	46
11	97	62	92	64
12	114	60	104	41
13	100	64	68	53
14	117	72	92	57
Mean (± SD)	**112 (± 12)***	**67 (± 6)^{A}**	**100 (± 23)*^{A}**	**55 (± 8)**

HRR= Heart Rate Reserve; bpm=Beat per minute; *$p \leq 0.05$; ^{A} $p \leq 0.05$

Figure 2.0: Heart Rate(bpm) vs. Age Rank* of Subjects at Low Intensity (40%).



*Age rank is by subject for all 14 subjects included in study. Youngest subject was assigned #1, continuing to oldest subject at #14.

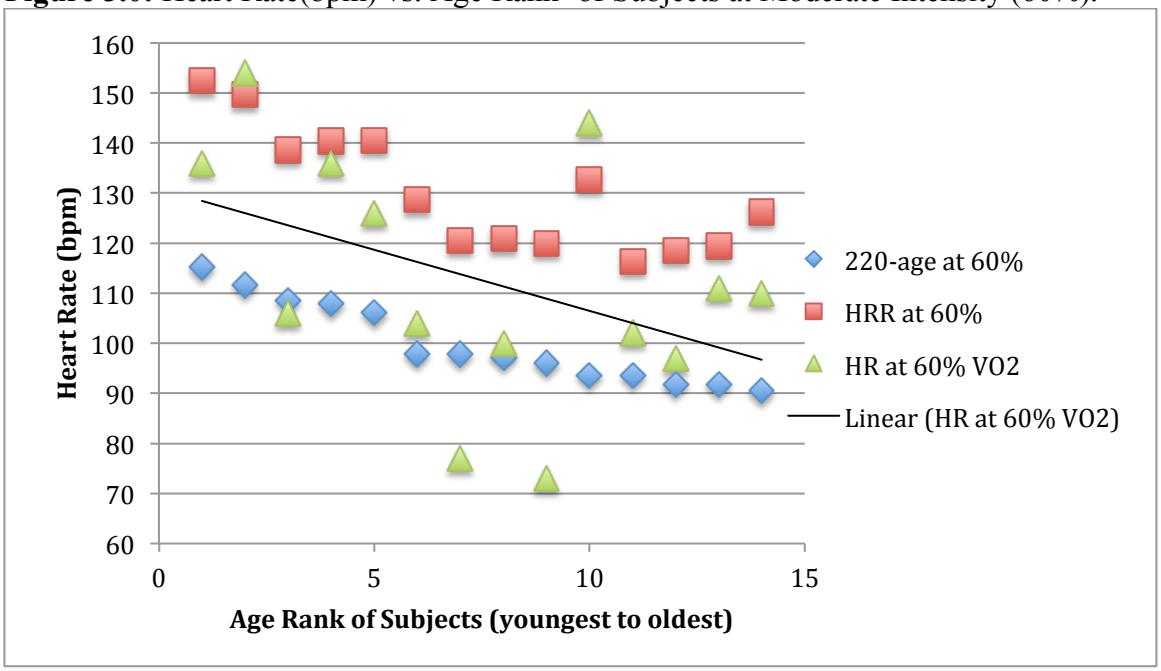
At 40% intensity, there was a significant difference between the heart rate reserve method and the heart rates derived from the percent of VO_{2peak} test (HRR=112±12, HR@VO_2=100±22, p=.000). At the low intensity of 40%, the HRR method overestimated HR when compared to the HR obtained from using the percent of VO_{2peak}. At 40% intensity, there was a significant difference between the 220-age equation and the heart rates derived from the percent of VO_{2peak} test (220-age=67±6, HR@VO_2=100±22, p=.026). At the low intensity of 40%, the 220-age equation underestimated HR when compared to the % VO_{2peak} calculation.

Table 3.0: Calculated HRs for Moderate Intensity (60%)

Subject	HRR (bpm)	220-age (bpm)	HR at % VO_{2peak} (bpm)	% True Max (bpm)
1	150	112	154	77
2	121	97	100	77
3	133	94	144	92
4	140	108	136	94
5	129	98	104	72
6	141	106	126	103
7	152	115	136	98
8	119	92	97	74
9	119	92	111	74
10	121	98	77	68
11	116	94	102	96
12	126	91	110	62
13	120	96	73	79
14	139	109	106	85
Mean (±SD)	**130 (± 12)***	**100 (± 8)**	**113 (± 24)***	**82 (± 13)**

HRR= Heart Rate Reserve; bpm=Beat per minute; *$p \leq 0.05$

Figure 3.0: Heart Rate(bpm) vs. Age Rank* of Subjects at Moderate Intensity (60%).



*Age rank is by subject for all 14 subjects included in study. Youngest subject was assigned #1, continuing to oldest subject at #14.

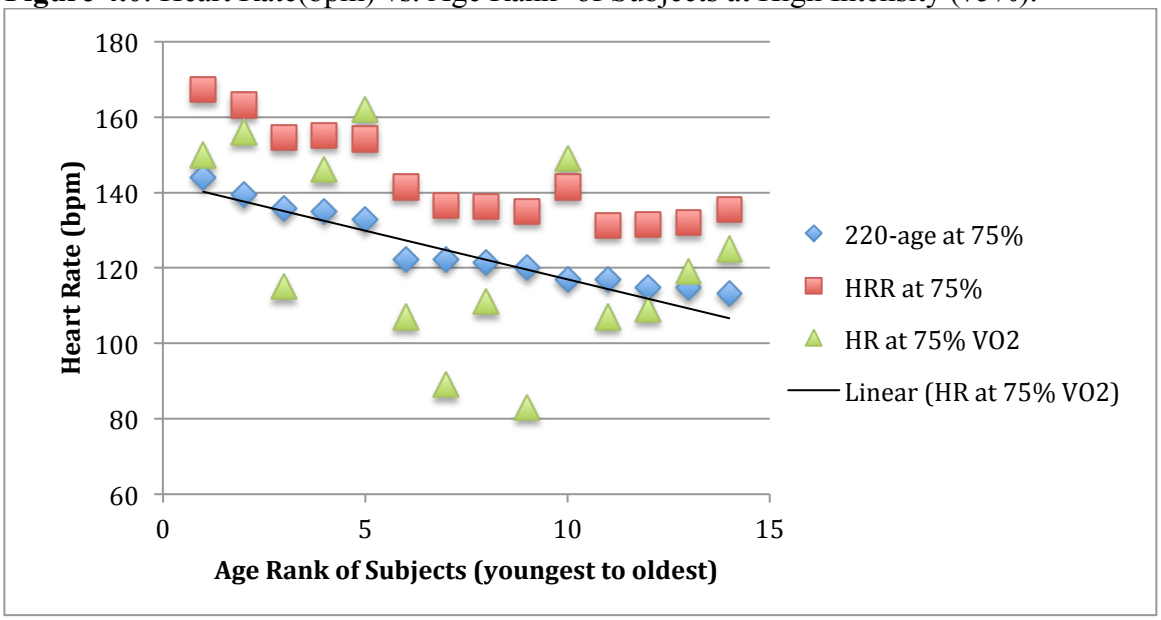
At 60% intensity, there was a significant difference between the HRs obtained from the heart rate reserve method and the heart rates derived from the percent of VO_{2peak} test (HRR=130±12, HR@VO_2=113±24, p=.004). At the moderate intensity of 60%, the HRR method overestimated HR when compared to HR obtained from calculating HR using the percent VO_{2peak}.

Table 4.0: Calculated HRs for High Intensity (75%)

Subject	HRR	220-age	HR at % VO_{2peak}	% True Max
1	163	140	156	96
2	136	122	111	96
3	142	117	149	116
4	155	135	146	117
5	142	122	107	90
6	154	133	162	128
7	167	144	150	123
8	132	115	109	93
9	132	115	119	92
10	137	122	89	86
11	131	117	107	120
12	136	113	125	77
13	135	120	83	99
14	155	136	115	107
Mean (± SD)	**144 (± 12)***	**125 (± 10)**	**123 (± 25)***	**103 (± 16)**

HRR= Heart Rate Reserve; bpm=Beat per minute; *$p \leq 0.05$

Figure 4.0: Heart Rate(bpm) vs. Age Rank* of Subjects at High Intensity (75%).



*Age rank is by subject for all 14 subjects included in study. Youngest subject was assigned #1, continuing to oldest subject at #14.

At 75% intensity, there was a significant difference between the heart rate reserve method and the heart rates derived from the percent of VO_{2peak} test (HRR=144±12, HR@VO_2=124±25, p=.003). At the high intensity of 75%, the HRR method overestimated HR when compared to HR obtained from calculating HR using the percent VO_{2peak}.

CHAPTER FIVE: DISCUSSION

Overview

In the acute leukemia population, the prescription of exercise is challenging due to not only the intense treatment schedules and side effects, but also the ability of hospitals to prescribe exercise based on cardiorespiratory testing. Not every hospital has the equipment and personnel to perform VO_2 testing on this patient population, thus requiring exercise intensity prescription to vary based on availability of testing methods. In previous studies, exercise prescriptions varied significantly. Some researchers used RHR+ 30bpm (Chang, 2007), 40-50% of HRR (Battaglini, 2009), and 60-75% of HRR (Alibhai, 2012). For the purpose of practicality in these hospital settings, the Heart Rate Reserve method and 220-age equation have been used in this population to prescribe exercise intensity without the benefit of a cardiorespiratory maximal exercise test. However, if one is looking for prescription with a great level of precision, to date, no study has examined the precision of using practical methods of exercise intensity determination such as the HRR or the 220-age equation in leukemia patients initiating treatment. Therefore, it is not known if using these exercise intensity practical quantification methods provide any useful information when used to promote exercise training adaptation in this cancer population. Therefore, the purpose of this study was to compare the heart rate values calculated from the Heart Rate Reserve and 220-age equations and the heart rate values obtained from the VO_{2peak} test for the determination of aerobic exercise intensity in acute leukemia patients undergoing induction chemotherapy.

The values from each of the three methods were compared at three different intensity levels: low (40%), moderate (60%) and high (75%). This study was unique in its comparison of the previously used methods of Heart Rate Reserve and 220-age equations to the gold standard method of VO_2 tests. The comparison of all three methods across several intensity levels allowed us to examine the accuracy of such calculated methods when compared to a gold standard method such as VO_2.

At the low intensity of 40%, the results indicated that both of the methods were significantly different from the HRs derived from the VO_{2peak} test and thus neither was an acceptable method for determination of aerobic intensity. After studying the individual HRs of the subjects, the wide range of heart rates responses was probably the main reason for the non-significant findings observed in the current study. It is also important to note, that this was an evaluation of different methods of exercise intensity quantification using one single exercise bout performed to maximal effort. Considering that HRs tend to vary significantly in this patient population, mostly due to different treatments effects on the patients physiology, HRs may not be the most appropriate way to prescribe training thresholds in this patient population.

The HRR overestimation when compared to the HR at $\%VO_{2peak}$ may be due to an increase in fluids, a decreased hemoglobin capacity or other physiological alterations due to the disease and treatment that can affect HRs. The underestimation by the 220-age equation may be due to the resting heart rate not being included in the calculation. In this population the resting heart rates were often above the estimated 220-age value at 40% thus leading to underestimation in all participants tested when compared to the HR at $\%VO_2$.

Due to these large differences, another method of exercise intensity determination could potentially be used such as a perceived rate of exertion. The physiological changes due to the treatment and its side effects may change the daily ability of this cancer population to perform physical work and a subjective measurement to ascertain how they feel and how they are able to perform on any given day may assist trainers and help care providers to quantify and monitor their exercise intensity until a better method of exercise quantification is explored.

At the moderate level intensity of 60%, there was no significant difference between the 220-age equation and the HRs derived from the VO_{2peak} test at 60% intensity despite a difference of 13 bpm between methods. This difference of 13 bpm is clinically significant and therefore the results of this study should be interpreted with caution. The 13 bpm lower HR produced by the 220-age equation is large enough to significantly compromise the accuracy of the exercise prescription by under-prescribing an intensity that is aimed to promote desirable changes in certain physiological parameters, such as cardiorespiratory fitness.

At the moderate intensity, the cardiorespiratory system is working harder to supply the muscles with oxygen more quickly to be able to maintain a higher level of force production. The increased cardiac output required at this intensity may cause the heart rates to become more similar to the predicted equations as their intensity level increases in order to maintain the higher level of output and compensate for reduced oxygen carrying capacity. The low sample size and nature of the study does not allow for this to be verified, but more participants are needed to determine if these inferences are potentially the reason for the HR differences.

The HRR method again overestimated when compared to the HRs from VO_{2peak}, just as it did at the low (40%) intensity. The reasons for this overestimation are likely the same as those for the low intensity – a decreased ability to carry oxygen as a result of the disease or the myelosuppression from chemotherapy.

At the high intensity of 75%, similar results to the moderate intensity were found. There was again no significant difference between the 220-age method and the HRs derived from the VO_{2peak} test, though at this intensity the difference between the means was only 2bpm, which confirms that at higher intensities, there is a diminished heterogeneity of HR responses between subjects due to a larger cardiac output needed for the subjects to be able to maintain this higher level of power output. As seen at the other intensities, the HRR method overestimated HRs when compared to the HRs derived from the HR% of VO_{2peak}.

Though the statistical outcomes at the moderate and high intensity levels were more favorable with the 220-age showing no significant differences, the overall picture when looking at individual participants is much different. Not only is there wide variation between the two prediction methods and the HRs from the VO_{2peak} test, but also the variation is not systematic or consistent between or even within participants. These erratic differences across intensities suggest that another method or scale might need to be included in the determination of exercise intensity in this specific population. As patients go through treatment, their exercise tolerance changes daily due to infections, fluids shifts, treatment side effects and the disease process itself. For practicality and scalability purposes without compromising prescription accuracy, a subjective parameter

based on the daily physical outlook of the participant might be used as a multiplier or scale to better judge intensity without relying solely on heart rate.

Based on the results of this study, in terms of direct application in a hospital setting, neither the HRR method nor the 220-age equation appear to be reliable methods for the determination of exercise intensity using HRs due to the high HR variations between patients at each level of intensity though statistically there was no difference shown using the 220-age equation at moderate and high intensity levels. The differences of 10-12 bpm between the equation and the actual HR from the VO_2 are substantial especially in this patient population which experiences changes in exercise tolerance depending on their cancer and its treatments. At this time and based on the results of this study, it is recommended that for this patient population, heart rate equations and heart rate in general should not be used exclusively to determine exercise intensity. As discussed above, including another parameter along with heart rate, or even testing another intensity determination method might produce more accurate results than those seen in this study. However, at this time only heart rate and RPE have been used in the previous studies to prescribe exercise and this is the first study to look at the accuracy of any methods so no positional statement as to the recommended method can be made at this time.

In a new study by Scott in 2014 there was significant HR and VO_{2peak} variability between two peak tests performed 5.6±5.5 days apart in early stage prostate cancer patients. In terms of HR, the mean difference between tests was not large but the variation for some individual participants was as great as 15bpm. Physiologically heart rate can be affected by a variety of factors including fluid levels, stress, medications, and

others. Due to the fact that the main objective of exercising ALP during treatment is the maintenance of overall physical function, and the attainment of a training response is not always possible, for patients experiencing less treatment-related side-effects, a training progression aiming to produce more prominent positive response should potentially be explored; therefore future studies must be conducted to examine the most appropriate and precise way to prescribe the training dose to promote a more specific physiological responses. It may be, that for this cancer population, functional training including more of a resistance training focus would be more appropriate and the cardiovascular component of the overall fitness and health of the subject be maintained with light doses of aerobic training where the intensity determination may be done based on each patient's capacity determined on a daily basis. Therefore, it is paramount that future studies examine different training protocols, with different exercise intensities, along with the examination of more appropriate ways of quantifying exercise intensity, specially aerobic training, in this very unique cancer population of ALP.

Study Limitations

As mentioned prior, the sample size for this study was small. Preliminary analysis of the first 9 patients collected indicated HRR as a better prediction method than 220-age at all intensity levels. However, the addition of just the final 5 patients was enough of a difference to change the statistical outcomes to favor the 220-age equation at moderate and high intensities. Therefore, a larger sample size appears to be needed so more definite conclusions can be made on the prescription of aerobic exercise intensity using HR in this cancer population.

Within the acute leukemia participants group for this study, there was variation in age, 28 to 69 years old, as well as large differences in resting heart rate values from 57 to 98 beats per minute. Some of these heart rate values may also have been different based on factors such as medications and starting of treatment prior to completion of the VO_{2peak} test. Out of the 14 patients tested, one was on medication that suppressed their heart rate and blood pressure, which affected both the resting and exercise heart rate values. This was due to the levels of stress and anxiety exhibited by the patient prior to enrollment and not to a cardiovascular comorbidity. He was cleared to participate in the study and experienced no adverse effects during testing.

Since this study was developed as a preliminary examination of alterations in HR and its influence on training threshold determination using data from a larger trial designed to evaluate other outcomes, a future experiment should focus specifically on the HRs and potential alterations HR may have during treatment. Nevertheless, the result of this study may be used to inform the calculation of power for future trials so the results of this preliminary study can be confirmed or refuted.

Recommendations for Future Research

First, this study should be continued or replicated with a larger sample. It is also recommended that this study design should be used in other cancer populations to determine appropriate methods for determination of aerobic exercise intensity. The differences in treatment as well as the disease processes may cause their heart rate and cardiovascular response to vary from those seen in acute leukemia patients. Therefore it is recommended that future studies should evaluate the influence of these factors on HRs responses not only in ALP but also in other cancer populations.

At this time, heart rate continues to be one of the most practical methods to prescribe and track exercise intensity in hospitals and other settings where more precise methods used in laboratory research such as prescribing exercise based on the results of VO_{2max} testing or from lactate profiling are not available or even feasible. Since HR variations are commonly observed not only in cancer patients but also in athletic populations, the use of HR in the medical setting should be used more as a monitoring method to increase the safety of patients while exercising. Other methods of aerobic exercise intensity quantification, such as the creation of methods that encompasses physiological and patient rated exercise tolerability feelings may prove in the future to be a better option for patients whose physical and functional capacities vary significantly day to day.

Conclusion

Based on the results of this study, of the heart rate methods, the 220-age equation was not significantly different from the HRs at $\%VO_{2peak}$ for the moderate and high intensities. However, the differences between the methods both between and within patients at all intensities studied leads to the conclusion that neither the heart rate reserve method or 220-age equation should be solely used to determine exercise intensity in this population. The exploration of other parameters and methods to be used alone or in conjunction with heart rate to better determine physical exertion during induction chemotherapy is recommended.

APPENDIX 1.0: EXERCISE PRESCRIPTIONS OF PREVIOUS STUDIES

Study author & year	Aerobic exercise	Intensity & measurement
Chang et al, 2007	Ex grp: Walking in hallway 3 wk program	12min, 5x/wk Int: RHR + 30 bpm
Battaglini et al, 2009	2 bouts/sess (AM & PM) 5-10min cycle or treadmill 5-15min resistance 5-10min core	3-4x/wk for 3-5wks Int: 40-50% HRR RPE <6 (1-10 scale)
Klepin et al, 2011	5-15min walking 15min strength & flexibility 5-15min walking	3x/wk for 4wks *offered Int: Mild (walking) RPE avg = 10.5 (6-20)
Alibhai et al, 2012	10-40min walk or bike 10-25min resistance 5-10min flexibility	4-5x/wk during induction trmt Int: light to moderate RPE 3-6 [or HRR 50-75%]

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