PREDICTING MAXIMUM OXYGEN UPTAKE (VO_{2max}) USING A DYNAMICAL SYSTEMS MODEL IN ACUTE LEUKEMIA PATIENTS

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ABSTRACT

ERIN MCMULLEN: Predicting maximum oxygen uptake (VO_{2max}) using a dynamical systems model in acute myeloid leukemia patients.
(Under the direction of Claudio Battaglini)

PURPOSE: To determine if a dynamical systems model can estimate VO_{2max} using data from a CPET on a cycle ergometer in acute leukemia patients prior to treatment. METHODS: Seventeen patients performed a CPET. The VO_{2peak} obtained during the CPET and predicted values from the dynamical systems model were compared using paired samples t-tests. RESULTS: Significant differences between VO_{2peak} obtained during the CPET ((18.09 ± 4.89) p=.001) and dynamical systems prediction (22.45 ± 7.00 mL/kg/min) was observed. A significant correlation between the predicted and obtained values for the time series was observed (r (16) = 0.96 p <.05), while the model had a percent error of 25%. CONCLUSION: Since transient changes captured in VO_2 in response to the demands placed on the equilibria of the dynamical system, the system is not subject to the same physiological CPET limitations, potentially providing a more precise VO_{2max} determination.

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CHAPTER I
INTRODUCTION

Acute myeloid leukemia (AML) is a hematological cancer that results in the bone marrow producing abnormal red blood cells, white blood cells, or platelets (NCI, 2015). AML most commonly occurs in men over the age of 60, with a history of smoking, and a previous history of chemotherapy or radiation treatment (ACS, 2016). It is estimated that there will be over 60,140 incident cases of leukemia in the United States in 2016, of which 19,950 are expected to be AML. In 2014, U.S. cancer surveillance data showed that nearly half of the 24,400 reported leukemia mortalities were in patients with AML (ACS, 2016).

The most common initial phase of treatment for AML patients is inpatient induction chemotherapy. The objective of induction chemotherapy is to eliminate all cancerous cells from the blood and bone marrow. Patients are generally admitted to the hospital to receive intravenous chemotherapy for a week, followed by an extended inpatient recovery period lasting for 3-6 weeks (Alibhai, 2012). During this time, patients are susceptible to infections and unexpected bleeding and bruising due to low white blood cell counts and low platelets, respectively. Patients also experience a myriad of other negative side effects from chemotherapy treatment, including hair loss, nausea, vomiting, mouth sores, cachexia, general fatigue, and psychological symptoms such as depression and anxiety (Bryant et al, 2015; Zimmerman, 2013).

To date, there have only been a few studies that have explored the efficacy of exercise as a treatment modality to lessen the burden of treatment and mitigate the impact of the negative side effects to improve patient outcomes, functionality, and quality of life in this cancer population. Four prominent studies of exercise interventions have found consistent evidence of improved outcomes in AML patients. The first recorded exercise intervention in an AML patient population was an exercise program of five days of walking in one week (Chang, 2008) and found reduced fatigue, anxiety, depression, and improved walking distance (2008). In 2009, Battaglini et al. conducted an exercise intervention consisting of aerobic and resistance training twice daily, three days a week in 10 patients with acute leukemia. Aerobic exercise was conducted at 60% heart rate reserve (HRR).The authors reported reduced fatigue, depression, and increased cardiorespiratory endurance (Battaglini, 2009). Kleplin (2011) and colleagues conducted an exercise intervention that included four weeks of walking, stretching, and strength training. The authors found that physical function was maintained, while physical quality of life was improved. Most recently, in 2012, Alibhai et al. conducted a randomized clinical trial that included a progressive training program that was individualized to each patient. It consisted of flexibility and resistance training in addition to four to five days a week of 30-45 minutes of light to moderate aerobic exercise, defined as 50-75% HRR, or a rate of perceived exertion (RPE) of 3 to 6. Alibhai et al. observed reduced fatigue and anxiety, as well as improved aerobic fitness and physical functionality (2012). Given the existing evidence that exercise interventions are both feasible and beneficial within AML populations, proper exercise prescription is necessary to maximize exercise-training benefits.

According to the American Heart Association, cardiopulmonary functional capacity reflects an individual's ability to perform tasks of daily living as well as quantify exercise tolerance and is usually expressed as maximal oxygen uptake (VO_{2max}) (Arena, 2007). The gold standard way to assess cardiopulmonary function capacity is through a cardiopulmonary exercise testing (CPET) with indirect calorimetry. However, this type of testing requires expensive and specialized equipment, and trained personnel. Therefore, the assessment of cardiopulmonary function capacity is not always available in many different clinical settings, making it very difficult for clinicians, exercise specialists, and other health care professionals to benefit from using the results of such test for the initial assessment, prescription of exercise, and most recently, as a prognostic tool for post-treatment complications and mortality in certain cancer populations (Jones et al. 2010, Wood et al, 2013).

An alternative method that can be used for the assessment of VO_{2max} is to perform submaximal CPET and use the results of these types of tests to estimate $VO_{2max.}$ These types of tests are usually based on heart rate response and its relationship to different exercise intensities. By plotting the heart rate response during the final two stages of a submaximal test, and extrapolating the results using linear mathematical equations, one can estimate VO_{2max}. However, this relies on the assumption that HR will respond linearly to different increments of exercise intensity. Another assumption is that mechanical efficiency is the same for everyone. For these linear equations, data must be collected for a minimum of two test stages where HR achieved steady state between 115-150 beats per minute, significantly reducing the accuracy of the tests, even more so in populations where their physiology has been modified through disease or treatments.

Grant (1995) found that submaximal CPETs using a cycle ergometer under-predicted VO_{2peak} by 7.8 mL/kg/min. This estimate is not only outside the accepted standard error of measurement of 2 mL/kg/min, but clinically significant when considering using the results of such tests for the precise assessment of cardiorespiratory function or to use the results of such tests for the prescription of aerobic exercise.

While it is important to avoid overexertion within clinical populations that are sick or recovering from treatments, such as patients with hematological cancer, it is critical to conduct training at a level sufficient to elicit the response necessary to induce positive adaptations. This presents the need for a method to predict VO_{2max} with the precision of a max test, but with the limited effort of submaximal testing, so it can be available to clinicians, researchers, exercise physiologists and health care providers using aerobic exercise to improve the health and functionality, and use the results of such tests to inform better treatment practices.

Previous prediction models have tried to predict VO_{2max} using skinfolds and body mass index (BMI) instead of exercise testing (Jackson, 1990). The standard of error of these types of models are usually around 5.3 mL/kg/min with skinfolds and 5.6 mL/kg/min, with BMI. This was determined to be appropriate for 95% of the adult population, but is remains too variable for use in a clinical population.

In 2008, Stirling et al. developed a dynamical systems mathematical model to predict maximum VO_{2max}. The theory behind this type of model is that the cardiorespiratory system is always working to reach equilibrium between demand and cardiac output. There is an absolute minimum heart rate for each individual and a maximum heart rate that can theoretically be exceeded but is still physiologically limited, and a transient value that changes as a function of demands placed on the system (exercise). Mazzoleni, Battaglini, and Mann in 2015 (paper in review) further adapted this model to define demand as a function of power (Watts) and cadence pedaling on a cycle ergometer. In order to predict VO_{2max}, participants perform a submaximal exercise test and the subsequent values are entered into the model. The model calculates individual parameters that account for and are dependent on the values from the test. A genetic algorithm generates hundred of possible parameters and is run to determine the parameters that best fit the model. Through the application of the algorithm, the parameters are individualized to the person's performance during testing, and therefore removing the need for any physiological variables such as age, sex, and body mass as well as assumptions that all individuals respond the same physiologically to exercise such as heart rate and oxygen uptake responses. This initial approach tested in healthy young individuals using a cycle ergometer, showed promise, since it would estimate VO_{2max} with a level of precision much superior to currently submaximal CPETs and extremely accurately when compared to gold standard CPET.

Based on the preliminary results of Mazzoleni, Battaglini, and Mann (2015), math model prediction using dynamical systems, exploring this testing concept in a clinical population such as patients with hematological cancers, where physiological changes due to disease and treatment are constantly occurring, may provide insight on the true predictability of the model and will help further develop the model and protocols designed to be used not only in patients with hematological cancers but many different clinical populations.

Statement of purpose:

The purpose of this study was to determine if a dynamical systems model can accurately estimate VO_{2max} using data obtained during a maximal cardiopulmonary exercise test (CPET) performed on a cycle ergometer in acute myeloid leukemia patients prior to receiving induction chemotherapy treatment.

Research Questions:

R_1: Can a dynamical systems model accurately predict VO_{2max} in acute myeloid leukemia patients using all of the data obtained from a CPET prior to beginning chemotherapy treatment?

R_2: Can a non-exercise prediction equation accurately estimate VO_{2max} in acute myeloid leukemia patients using anthropometric data, body fat percentage or BMI?

R_3: Can a dynamical systems model more accurately predict VO_{2maxk} in acute myeloid leukemia patients data obtained from a CPET performed on a cycle ergometer than a non-exercise prediction equation?

Research Hypotheses:

H_1: There will be no significant difference in VO_{2max} values between the dynamical systems model estimation using all data from a CPET test and the VO_{2max} value attained during a CPET performed on a cycle ergometer.

H_2: There will be no significant difference in difference between the non-exercise equation predicted VO_{2max} using anthropometric data (percent body fat or BMI) from baseline testing and VO_{2peak} values attained during a CPET performed on a cycle ergometer.

H_3: There will be no significant difference between VO_{2max} values between the dynamical systems model estimation using all data from a CPET test and the VO_{2max} value estimated using a non-exercise estimation equation using percent body fat or BMI.

List of Abbreviations and Definition of Terms:

Acute myeloid leukemia (AML): A type of leukemia that affects the bone marrow and causes the production of abnormal red blood cells, white blood cells, or platelets (NCI, 2005).

Cardiopulmonary exercise test (CPET): Incremental or graded exercise test using indirect calorimetry to determine maximal oxygen consumption (VO_{2max}).

Maximal oxygen consumption (VO_{2max}): The body's maximal ability to intake and utilize oxygen, and remove waste products during exercise.

VO_2 peak: The highest oxygen uptake (VO_2) achieved by a patient during a CPET. For this study, the 3 highest values of oxygen uptake during the last stage of the CPET will be averaged to derived the maximal oxygen uptake value achieved during the tests and will be used for comparison with the math prediction model.

Dynamical systems model: Model consisting of differential equations for the underlying response pattern of oxygen uptake and utilization (Stirling, 2005).

Assumptions:

1. All patients followed pre-assessment guidelines prior to CPET.
2. All patients gave maximal effort during CPET.
3. The dynamical systems model determines the best set of individual parameters.

Limitations:

1. Relatively small sample size.
2. Generalizability to other clinical populations as well as general population.

Delimitations:

1. Patients over the age of 21.
2. Recently diagnosed with acute myelogenous or acute lymphocytic leukemia, but not yet receiving induction chemotherapy.
3. Approved by oncologist to participate in CPET.
4. No pre-existing condition or comorbidity that would increase the risk of performing CPET.

Significance of the study:

This model could be instrumental in prescribing more appropriate training intensities for exercise interventions in AML patients without having patients to undergo a maximal cardiopulmonary exercise test. The dynamical systems model allows for individualization of results, without needing to account for individual physiological differences because these differences manifest in their transient VO_2 responses at various power outputs and cadences during a CPET that are capture and incorporated in the prediction model. The individualization of the prediction provides more accurate estimation of VO_{2max} and MHR exercise, thus potentially improving one’s ability to more accurately prescribe exercise intensity for aerobic training programs. Within AML patients, the results of this initial study, may provide clinicians and exercise physiologists with a much more practical yet extremely precise way to prescribe aerobic exercise intensity to AML patients ensuring that these patients are exercising at a high enough threshold to induce adaptations, without over taxing the patient and potentially promoting blunted responses.

CHAPTER II

REVIEW OF LITERATURE

Cardiopulmonary Exercise Testing

Maximal oxygen consumption (VO_{2max}) is considered the best way to measure the capacity of the cardiovascular and pulmonary systems and assess aerobic capacity as well as physical fitness (Brooks, Fahey, Baldwin, 2005). The current gold standard method for measuring VO_{2max} is a cardiopulmonary exercise test (CPET). In 2003, the American Thoracic Society and American College of Chest Physicians released a joint statement on the use of cardiopulmonary exercise testing including indications for use, implementation, interpretation and clinical application. The purpose of this statement was to standardize measurements and provide guidelines for testing, as well as the interpretation of results. The American Heart Association also released a statement on conducting exercise testing that provides guidelines for certain clinical populations and focuses on the diagnostic and prognostic purposes of conducting a CPET (2007). These statements attempt to standardize measurements due to the variation amongst exercise tests including mode of exercise used protocol.

Due to the variation among exercise tests, there are certain objective criteria that must be met to consider maximal oxygen consumption achieved to be VO_{2max}. These criteria propose that the exercise method used must utilize at least 50% of the total muscle mass and be continuous and rhythmical (walking, running, cycling) for an extended period of time. Additionally, results must be independent of motivation or skill and performed under standard experimental conditions. In order to determine that an individual has achieved their maximum capacity, they must meet at least three of the following criteria: a high rate of perceived exertion, a respiratory exchange ratio exceeding 1.1, a blood lactate level greater than 8 mmoles, a plateau of VO_2 even with increasing workloads, or a heart rate within 10 beats per minute of the age-predicated maximum heart rate (Powers, 2012). If the criteria for reaching VO_{2max} have not been met, then the highest attained VO_2 is considered the $VO_{2peak.}$

Prognostic Value of VO_2

Kavanagh, Mertens, and Hamm (2002) examined the predictive efficacy of exercise capacity measured directly by VO_{2peak} in men participating in cardiac rehabilitation following cardiac incidents. This study consisted of the largest sample and longest follow-up period to date in a study of men referred for cardiac rehabilitation. The authors found that exercise tolerance was the primary predictive factor in all-cause mortality, with mortality decreasing substantially by fitness level. The authors concluded that improving aerobic power could enhance functional capacity and overall survival. Recommendations for further study include exploring the prognostic applications of aerobic exercise in women. These findings were supported by Myers et al. (2002) in a study examining the prognostic effect of exercise capacity amongst all men, healthy and those with previous cardiac conditions to determine if it is an accurate predictor for all mortality including healthy populations. They found after accounting for age, METS was the single largest predictor of mortality. Each MET was associated with a 12% increase in survival.

In 2008, Jones et al. performed a systematic review of cardiorespiratory exercise testing in clinical oncology, according to the guidelines set forth in the ATS/ACCP statement. Of 852 potential citations, 90 were included in the review. Most of the reviewed studies involved operable disease, where testing was performed prior to surgery, and the majority of patients were women. In studies involving interventions, they were generally conducted during or after treatment. The authors concluded that in general, CPET was not optimum for these populations and data reporting standards did not comply with national guidelines. Suggestions for further research include standardizing guidelines for exercise testing for patients with cancer.

In 2010, Jones et al. performed a prospective multisite study to assess the potential prognostic benefits of VO_{2peak} in 398 non-small cell lung cancer (NSCLC) patients. The authors adjusted their results for age, sex, and all-cause mortality, and found that VO_{2peak} was a strong predictor of survival. The underlying physiological mechanisms are unclear, but the authors suggest a possible explanation is an inverse relationship between cardiovascular performance and cardiovascular disease, as well as muscle atrophy and muscular endurance. The results of this study suggest that VO_{2peak} can be a predictor of mortality, and improvement in VO_2 should be a goal to improve post-treatment outcomes. In a subsequent study in the same population, Jones examined the prognostic value of functional capacity and exercise in NSCLC patients (2012a). Patients performed a six-minute walk test and completed a questionnaire about their exercise habits. Functional capacity was found to be an independent predictor of all-cause mortality. Exercise behaviors were also associated with reduced mortality risk. Findings support functional capacity as a prognostic tool, and the authors recommend further research into the efficacy of implementing exercise training to improve functional capacity.

Jones et al. also assessed VO_{2peak} in four cohorts of breast cancer survivors: before treatment, during treatment, after adjuvant therapy for non-metastatic disease, and during treatment for metastatic disease (2012b). The authors' previous conclusions were supported by the results seen in this cancer population. They observed that women had significantly impaired cardiovascular function across all groups compared to healthy aged matched sedentary women. One third of the study population had a VO2max below the capacity required for functional independence (15.4 ml/kg/min). They also concluded that VO_{2peak} might be a predictor of survivorship in metastatic disease, as patients with a VO_{2peak} greater than or equal to 15.4 mL/kg/min had a higher probability of survival compared to patients with VO_{2peak} less than 15.4 mL/kg/min

Current Issues with Cardiopulmonary Testing

An issue with performing cardiopulmonary exercise testing in clinical populations is the inherent limitations of various body systems due to the diseased state. Palange et al. (2007) investigated cardiopulmonary exercise testing as a diagnostic tool for measuring functional capacity, assessing shortcoming, tracking disease progression, and for prognostic prediction in clinical populations. They discussed how CPETs could be used for differential diagnosis to pinpoint specific areas of dysfunction in cardiopulmonary fitness, specifically focusing on the system that is the limiting factor. Some of these factors include alveolar gas exchange, oxygen delivery, oxygen uptake at the muscle, and deconditioning. The authors appraised the diagnostic power of CPET for various diseases and dysfunctions and gave recommendations for exercise testing of clinical populations.

In addition to the inherent limitations of maximal testing within specific clinical populations, it can also be resource-prohibitive due to the need for specialized equipment, trained personnel, and considerable time and space. Submaximal testing can be conducted to reduce these constraints, but results in a loss of precision. Thus, there is a need for increased precision of maximal predictions derived from submaximal testing. In an attempt to address this lack of precision, Montoye et al. developed a multiple linear regression model to predict VO_{2max} using output from submaximal testing as predictor variables (1986). They utilized a submaximal cycle ergometer test, a graded maximal treadmill test, and nonexercise data in their model. The authors determined that perceived functional ability (PFA) was the most statistically significant predictor of VO_{2max}. They also found that their model was statistically more accurate than the YMCA bike protocol for the estimation of VO_{2max}. Montoye et al.'s model accurately predicted VO_{2max}, and was more precise when non-exercise variables were included.

Non-exercise VO_2 Prediction Equations

More recent studies have also utilized multiple regression analysis to predict VO_{2max}. Nes et al. developed a non-exercise model for predicting VO2max using data from 4,637 male and female participants of the HUNT study, a longitudinal population health study in Norway They used data splitting to cross-validate the model using different subsets of subjects and found that the model was accurate in predicting VO_{2peak} in these healthy populations. The major predictors of VO_{2peak} included age, weight, waist circumference, resting HR, and leisure time physical activity. This model could be important for predicting VO_{2peak} in a non-clinical setting when exercise testing is not feasible (Nes, Janszky, Vatten 2011).

In a subsequent study using data from the HUNT study, Nes et al. (2014) used previously established model to predict all-cause mortality among cardiovascular disease patients. They found that cardiorespiratory fitness was inversely related to mortality amongst men and women at baseline, after adjusting for potential confounders. These findings support the predictive nature of the model and its application for healthy or at-risk populations.

Dynamical systems Mathematical Prediction Models

In 2008, Stirling developed a non-exercise mathematical based prediction model. Stirling's is a dynamical model of heart rate kinetics for predicting heart rate response to exercise. The model gives physiological information about the subject based on oxygen uptake and heart rate response as a function of time and intensity at all exercise intensities based on physiological principals. One potential limitation of this study is that it does not account for individual variability in heart rate response to exercise by only examining constant intensities.

Mazzoleni, Battaglini, and Mann (paper in review) developed a nonlinear model to predict heart rate dynamics across a varying range of exercise intensities, in order to account for an individual's transient heart rate responses. The authors' model builds on Stirling's original model using cycling but includes a drive function of power (Watts) and cadence. The model includes parameters that are related to the individual's physiology, allowing the model to be individualized to each patient. Their model was capable of predicting heart rate at various transient exercise intensities accurately and showed that it was able to account for individual differences in physiology when making predictions. They also confirmed that heart rate can be more accurately predicted by power output and cadence than power output alone, what previous models used. A separate dynamical systems model is able to use the same functions and parameters and can be applied to VO_2 in order to predict maximal oxygen uptake.

CHAPTER III
METHODOLOGY

Population

The study population included seventeen patients recently diagnosed with acute myelogenous or acute lymphocytic leukemia, who had participated in the Exercise and Quality of Life in Leukemia/Lymphoma Patients (EQUAL) phase II study. Patients included men and women between 28 and 69 years old. Eligible patients were admitted for induction chemotherapy treatment within 3 days of beginning treatment. Patients were informed of the EQUAL phase II study by their oncologists and approved to participate before being contacted by a research team member. Upon receiving further information regarding the study and agreeing to participate, patients signed an informed consent approved by the Lineberger Comprehensive Cancer Center Protocol Review Committee (LCCC 1234) and the University of North Carolina Institutional Review Board (IRB).

The inclusionary criteria for the EQUAL phase II study included: (1) at least 21 years old, (2) recently diagnosed with acute leukemia, (3) approved by an oncologist to participate in cardiopulmonary exercise testing (CPET), and (4) able to read and understand English. Exclusionary criteria included any pre-existing conditions that would increase the risk involved of performing CPET such as: cardiovascular disease, respiratory disease, musculoskeletal disorders and disease, and/or altered mental or psychological state that could affect understanding the informed consent. Exclusion from being eligible to participate in the study was determined by reviewing the patient's medical history questionnaire and consulting with the patient's oncologist.

The medical history questionnaire completed by patients prior to participation included a general medical history, as well as a detailed cancer history including previous and planned treatment. Prior to participating in the CPET, patients underwent a complete physical examination including a resting ECG and a Multigated Acquisition Scan (MUGA) to assess cardiovascular function.

Instrumentation

Maximum oxygen uptake (VO_{2max}) and for those patients who weren't able to achieve VO_{2max} (VO_{2peak}) and MHR achieved during the CPET will be used in this study from the initial cardiopulmonary test administered to these patients enrolled in the EQUAL phase II trial. CPET tests were performed using a cycle ergometer (Monark 874E, Goteborg, Sweden). Heart rate was measured using a Polar heart rate monitor (Polar Electro Inc., Lake Success, NY) and was recorded every 10 seconds. Blood pressure was assessed by auscultation using a sphygmomanometer (American Diagnostics Corporation, Hauppage, NY) and a Littman stethoscope (3M, St. Paul, MN). Oxygen uptake was measured via a portable metabolic gas analysis system (Cosmed Portable K4b2, Rome, Italy). At the end of each stage and at the end of the test, the patient used the Borg Rate of Perceived Exertion (RPE) scale (6-20) to determine rate of perceived exertion. Data from the CPET will be used for estimations of VO_{2max} and MHR using dynamical systems modeling thought differential equations and will be processed and analyzed using MatLab R2014a (MathWorks, Boston, MA) on a computer (Valkyrie 17334, IBuyPower, Industry, CA).

Research Design

This study used data from the EQUAL phase II trial (IRB # 13-1082), a pilot randomized clinical trial designed to test the effects of exercise on the alleviation of multiple treatment related side-effects commonly developed in acute leukemia patients undergoing cancer treatments, including fatigue, loss of body mass with significant loss of muscle mass, depression, anxiety; which are common side-effects observed in this cancer population during induction phase of treatment along with other side-effects that occurs in a more patient specific basis . These side effects are known to significantly reduce the quality of life of this cancer population. All patients enrolled in the EQUAL phase II trial, underwent a CPET test prior to beginning chemotherapy treatment. The heart rate (HR) and oxygen uptake data obtained during the CPET were used to devise an estimation of maximum VO_2 using mathematical modeling (dynamical systems) and compared to the maximum values obtained from the CPET for oxygen uptake.

General Procedures

Upon being determined eligible for the study and cleared by an oncologist to participate, the EQUAL phase II study, the study procedures were explained in full to all patients, and if interested in participating in the study, patients were asked to sign an informed consent form. The study protocol included a number of baseline physical, functional, and psychosocial assessments, however, only data obtained from CPET (Oxygen uptake and HRs collected during the test) will be used for the current study. Patients enrolled in the EQUAL phase II study were randomized into a standard treatment control group, and an intervention group. However, because baseline assessments were completed prior to receiving treatment, this study used CPET data from all patients regardless of group assignment.

Cardiopulmonary Exercise Test (CPET)

Before beginning the CPET, patients were fitted with a facemask to collect respiratory exchange gases. Patients were also familiarized with the cycle protocol and the stationary cycle ergometer; and the seat was adjusted at approximately 120° of extension between the thigh and the lower leg. The protocol used was previously shown to be appropriate for determining cardiopulmonary capacity in cancer patients (Jones et al, 2009). Prior to beginning the test, resting VO_2 measurements were taken for two minutes while the participant was seated on the bike. This was followed by a two minute warm up, a period where patients pedaled at a cadence of 50 revolutions per minute (RPM) with a resistance of zero Watts (W). The cadence of 50 rpm was held constant for the duration of the CPET. Following the warm up, the initial workload was set at 25 Watts. The workload increased every minute by 5 to 20 W depending on the patient response during the warm up phase of the test, until volitional fatigue was reached at the end of the test. The criteria for test termination included: volitional fatigue, respiratory exchange ratio (RER) exceeding 1.10, or limitation by physical symptoms. The test was immediately terminated if the patient experienced chest pain, dizziness, nausea, if there were ischemic changes on the ECG, BP response was abnormal, or arterial oxygen saturation was 85% or less. Throughout the test, HR, BP and VO_2 were measured, with RPE taken at the end of every stage and at the end of the test. Maximum oxygen uptake was determined by averaging the three highest values of oxygen uptake during the last minute of the test. Patients completed a cool down period of 10 W resistance at their own pace until their HR dropped below 120 bpm.

Oxygen Uptake Data

The oxygen uptake collected every 4-breaths throughout the entire CPET will be used for the prediction of maximum oxygen uptake using system dynamics. Furthermore, oxygen uptake responses from the first two stages of the test will also be used for the prediction of maximum oxygen uptake using system dynamics and will be compared to the maximal oxygen uptake achieved by subjects during the CPET.

Dynamical systems Prediction Model

The mathematical model used for this study builds upon the work of Stirling and Zakynthinaki (2008), who used dynamical systems theory and physiological insight to construct a model for predicting oxygen uptake and heart rate responses of individuals based on system equilibrium. Their model is able to account for the nonlinear nature of oxygen uptake response across a range of constant exercise intensities, but does lacks the ability to predict across transient exercise intensities. The current model by Mazzoleni, Battaglini, and Mann (2015), expands on their model by developing a state equation for oxygen uptake demand and the addition of a multi-variable exercise intensity function. This model demonstrates that oxygen uptake is more accurately predicted by a combination of power output and cadence. Due to the nonlinear nature of this problem, a heuristic algorithm was developed for the parameter estimation. The parameter estimation algorithm was verified using synthetic data and then applied to oxygen data collected from laboratory cycling test performed on several healthy, regularly exercising adults. The resulting model predictions of the oxygen uptake responses showed good agreement with the experimental data ($R^2 = 0.92 \pm 0.04$). Additionally, the experimental results verified that exercise intensity during cycling is a nonlinear function of both power output and cadence. This mathematical model can also be used to determine the maximal oxygen uptake of an individual by utilizing the heuristic parameter estimation algorithm that was developed for making model predictions. The equilibrium-based model construction allows for the algorithm to estimate maximal oxygen uptake with a high degree of accuracy when transient effects in the oxygen uptake response are observed.

Statistical Analysis

All statistical analysis were performed using SPSS software (IBM, Durham, NC) and an alpha level was set *a priori* at $p < .05$.

Descriptive statistics, means and standard deviations, were calculated for maximum oxygen uptake achieved during the CPET and for the mathematically predicted value derived from system dynamics and the non-exercise prediction equation using BMI and body fat percentage. Maximum oxygen uptake attained from the CPET was compared to the predicted values from the dynamical systems model and the non-exercise prediction model using dependent samples t-test.

Power calculations may not directly apply to this study, since the mathematical models can achieve a high level of precision with only one subject. However, to prove that the model can also be used to predict maximal oxygen uptake with a high level of precision, such as in a cohort of patients where physiological alterations due to disease and treatment are expected to be extremely heterogeneous, data from 14 subjects was used in this study, for all comparisons between actual data collected from the CPETs and the predicted maximal oxygen uptake and MHR derived from dynamical systems model.

CHAPTER IV
RESULTS

Overview

The purpose of this study was to determine if a dynamical systems model can accurately estimate VO_{2max} from data obtained during a maximal cardiopulmonary exercise test (CPET) performed on a cycle ergometer in acute myeloid leukemia patients prior to receiving induction chemotherapy treatment. Due to patients not truly reaching their maximum oxygen uptake during the CPET test based on recommended criteria for attainment of maximum oxygen uptake describe in the methods section, the term VO_{2peak} was used to denote the maximum oxygen uptake attained by the patients during the CPET. The secondary purpose was to compare VO_{2peak} attained during a maximal cardiopulmonary exercise test to a non-exercise VO_{2max} estimation equation that includes BMI or body fat percentage. The tertiary purpose was to evaluate if there was a significant difference between the dynamical systems model predicted VO_{2max} and the VO_{2max} estimated from the non-exercise equation using percent body fat and BMI. Exploratory analyses were also conducted to capture the inter-variability between subjects that were not captured with absolute values between the non-exercise estimations, the dynamical systems model and the experimental values obtained. All data were analyzed using the statistical software SPSS, version 23 for Mac. Alpha level was set *a priori* at 0.05 for all main analyses. Descriptive statistics are presented in the form of means and standard deviations.

Subjects

Seventeen subjects were recruited from the EQUAL phase II clinical trial at UNC Lineberger Comprehensive Cancer Center and completed the baseline assessment including a CPET to assess cardiopulmonary function. All seventeen patients were included in the data analysis. One patient was missing body fat percentage calculation; therefore, a mean substitution was imputed for this missing value and used for the calculation of the estimated VO_{2max} using the non-exercise equation. Patient characteristics are presented in Table 1.

Table 1: Anthropometric Characteristics of Patients, N=17 (mean ± SD)

Characteristics	Baseline
Age (years)	53 ± 15.3
Height (cm)	171.8 ± 14.9
Weight (kg)	86.1 ± 20.2
BMI	29.3 ± 6.6
Body Fat %	30.2 ± 7.0

Paired samples t-tests were used to compare the dynamical systems model estimated VO_{2max} and non-exercise estimated VO_{2max} to maximum oxygen uptake obtained during the CPET. Descriptive statistics for VO_2 values are presented in Table 2.

Table 2: Descriptive Statistics for maximum oxygen uptake obtained during the CPET, Dynamical systems model, and non-exercise estimation equations (mean ± SD)

	mL/kg/min	L/min
VO_{2peak} obtained during CPET	18.09 ± 4.89	1.54 ± 0.57
Dynamical systems model estimated VO_{2max}	22.45 ± 7.00*	1.92 ± 0.78*
Non-exercise estimation VO_{2max} including BMI	19.91 ± 7.78	1.66 ± 0.59
Non-exercise estimation VO_{2max} including percent body fat	21.49 ± 5.92*	1.85 ± 0.63*

*<.05=significant different from VO_{2peak} obtained during the CPET.

Hypotheses

Hypothesis 1, there will be no significant difference between the dynamical systems model VO_{2max} estimation using all data from a CPET test and the VO_{peak} value attained during a CPET performed on a cycle ergometer. A significant difference ($p < .001$) was found between VO_{2peak} attained during the CPET and dynamical systems model predicted VO_{2max}.

Hypothesis 2, that there will be no significant difference between the non-exercise equation predicted VO_{2max} using anthropometric data (percent body fat or BMI) from baseline testing and VO_{2peak} values attained during a CPET performed on a cycle ergometer. A significant difference ($p < .005$) was found between VO_{2peak} attained during a CPET performed on a cycle ergometer and the non-exercise equation using percent body fat predicted VO_{2max} . There was no significant difference between VO_{2peak} attained during a CPET performed on a cycle ergometer and the non-exercise equation using BMI predicted VO_{2max} .

Hypothesis 3, that there will be no significant difference between VO_{2max} values between the dynamical systems model estimation using all data from a CPET test and the VO_{2max} value estimated using a non-exercise estimation equation using percent body fat or BMI. There was no significant difference between dynamical systems model predicted VO_{2max} and estimated VO_{2max} using percent body fat or BMI.

Exploratory Analysis

Exploratory analyses were conducted to capture the inter-variability between subjects that was not captured when analyzing the data using absolute values. The VO_{2max} values attained from the dynamical systems model and the non-exercise estimation equations were compared to the maximum oxygen uptake attained during the CPET data for each subject and expressed as percent difference from the "gold standard" CPET attained value. These values are listed in Table 3 as ml/kg/min ± percent change from the $VO_{2peak.}$

The dynamical systems model overestimated maximum oxygen uptake by 25.28% (± 27.20) while the non-exercise equation including percent body fat overestimated maximum oxygen uptake by 15.20% (±39.33), and by 26.21% (±40.75) when including BMI and body fat percentage respectively, when compared to the gold standard maximum oxygen uptake (VO_{2peak}) attained during the CPET. Correlational analyses were used to analyze the relationship between the model predicted and experimental VO_2 values over the duration of the CPET. The correlation was statistically significant, R^2=0.92.

Table 3. VO_2 Prediction Values as Percent Error

Subject	CPET VO_{2peak}	Model Predicted VO_{2max} ± % Δ	Equation Estimated VO_{2max} BMI ± % Δ	Equation Estimated VO_{2max} Body Fat ± % Δ
1	19.25	19.68 (+2.23%)	21.46 (+11.51%)	26.78 (+39.10%)
2	18.41	24.92 (+35.37%)	25.95 (+40.93%)	28.08 (+52.50%)
3	22.60	23.11 (+2.26%)	8.00 (-64.61%)	13.08 (-42.11%)
4	25.11	32.36 (+28.89%)	11.91 (-52.59%	19.66 (-21.69%)
5	16.33	16.40 (+0.42%)	13.59 (-16.84%)	23.84 (+45.95%)
6	22.83	25.08 (+9.86%)	29.25 (+28.14%)	32.91 (+44.18%)
7	11.62	20.62 (+77.55%)	12.97 (+11.64 %)	17.25 (+48.50%)
8	15.39	18.21 (+18.30%)	21.01 (+36.50%)	20.78 (+35.04%)
9	22.49	35.62 (+58.39%)	15.53 (-30.95%)	14.70 (-34.63%)
10	14.43	14.49 (+0.42%)	14.38 (-0.37%)	13.01 (-9.87%)
11	21.29	22.67 (+6.51%)	21.93 (+3.00%)	22.65 (+6.37%)
12	12.95	22.76 (+75.72%)	21.00 (+62.13%)	21.48 (+65.79%)
13	18.01	29.33 (+62.83%)	23.07 (+28.11%)	18.50 (+2.73%)
14	24.18	30.90 (+27.75%)	39.59 (+63.72%)	29.15 (+20.54%)
15	6.68	7.45 (+11.59%)	11.68 (+74.90%)	14.95 (123.79%)
16	17.40	17.50 (+0.61%)	24.18 (+38.97%)	21.49 (+23.52%)
17	18.50	20.56 (+11.13%)	22.97 (+24.18%)	27.0 (+45.93%)

CHAPTER V
DISCUSSION

Acute myeloid leukemia is a hematological cancer that results in the formation of abnormal red and white blood cells and platelets from the bone marrow and occurs in over 54,000 new patients each year (ACS, 2014). The initial stage of treatment includes inpatient induction chemotherapy for a week, followed by several weeks of inpatient recovery. During this time, patients are extremely susceptible to infections, bleeding, and bruising in addition to numerous of other negative physical and psychological symptoms associated with their chemotherapy treatment and reduced physical activity, including cachexia, fatigue, anxiety, depression, and sleep disturbances within many others.

Currently, there have been four studies that have examined the efficacy of exercise interventions in this population with the goal of mitigating the symptom burden, improving patient outcomes such as functionality and quality of life. All four studies found that exercise with this population is not only safe but also feasible and efficacious in alleviating the common physical and psychological decline experience by the majority of patients. The first ever program in this population reported reduced fatigue, anxiety, depression and improved walking distance in response to walking five days per week (Chang, 2008). An exercise intervention consisting of aerobic and resistance training twice daily, three days a week reported reduced fatigue, depression, and increased aerobic fitness (Battaglini, 2009). An intervention consisting of four weeks of walking, stretching, and strength training reported maintenance of physical function and improved quality of life (Keplin, 2011). Most recently, a randomized clinical trial consisting of a progressive training program individualized to each patient comprising of flexibility, aerobic, and resistance training four to five days a week, observed reduced fatigue and anxiety, as well as improved aerobic fitness and physical functionality (Alibhai, 2012).

While all studies to date have demonstrated the desired positive outcomes, the exercise interventions varied drastically from study to study in terms of exercise prescription and exercise modality. Due this heterogeneous body of literature examining the effects of exercise in leukemia patients, if is not possible at this time to make precise recommendations regarding the best and most efficacious prescription of exercise to maximize the benefits of exercise to this cancer population. Exercise interventions must be prescribed in a way that will maximize the physiological and psychological benefits without overtaxing the body and placing an undue burden on the patient. In order to properly prescribe an exercise program for an individual patient, there must be a standardized and objective method for assessing a patient's current physical fitness and prescribing exercise in relation to this measurement.

An individual's cardiopulmonary functional capacity expressed as maximum oxygen uptake (VO_{2max}) is an individual's ability to uptake and utilize oxygen during exercise and reflects an individual's ability to perform tasks of daily living as well as tolerate exercise (Arena, 2007). Cardiopulmonary functional capacity is considered among exercise physiologists as the single best measurement of overall fitness of an individual. Once an individual's VO_{2max} is known, exercise can be prescribed as a percentage of this number, typically in terms of a corresponding heart rate due to the nature of the relationship between heart rate and $VO_{2.}$ Some studies have shown that VO_2 is an independent predictor of mortality in different cancer populations (Jones et al. 2010, Wood et al., 2013).

The gold standard method of measuring VO_2 is through a cardiopulmonary exercise test (CPET) using indirect calorimetry. However, these tests require expensive and specialized equipment and personnel and may not be feasible or practical in all settings. An alternative to this, is to perform a submaximal exercise test and use the results to estimate $VO_{2max.}$ This method utilizes the relationship between heart rate and various exercise intensities, however, it is dependent on the assumption that an individual's heart rate will respond linearly to incremental exercise, and that mechanical efficiency is similar among different individuals. These submaximal predictions require an individual to achieve steady state in two stages during the exercise test, and due to the assumptions mentioned above, significant error of estimation is known to occur in different populations. In cancer patients such as those being treated for leukemia, the accuracy of submaximal tests are may be even more pronounced. In leukemia patients, due to the negative effects of the disease and treatment on the patient's physiology, the patients' exercise response most likely will violate submaximal testing assumption of estimation, leading to even more error of estimation. Non-exercise VO_2 prediction models have also been developed using skinfolds and BMI, with a standard error of 5.3 and 5.6 mL/kg/min respectively when compared to the gold standard CPET (Jackson, 1990). While this method would be acceptable for certain healthy adult populations, its use in clinical populations such as cancer has been very little evaluated if evaluated at all.

Submaximal and non-exercise prescription models appear not to be the best alternative methods to estimate VO_{2max} in cancer patients due to assumptions that assume linear relationship between HR and VO_2, similar mechanical efficiency between patients, and altered physiology of patients due to their disease and treatments. However, to our knowledge, no study has evaluated to date the precision of these methods to be used as alternative to gold standard CPET in Leukemia patients.

Stirling (2005, 2008) developed a dynamical systems model of the heart rate and oxygen uptake responses to exercise. However, this model was limited in its application because it was only able to predict hear rate and oxygen uptake responses at constant exercise intensities. Mazzoleni and colleagues (2016) expanded upon this model and incorporated a demand function to capture the dynamics of the system at non-steady state and transient exercise intensities. They were also able to utilize this model to make predictions for the maximum heart rate and maximal oxygen uptake values of an individual. For the case of cycling, an individual performs a cardiopulmonary exercise test on a cycle ergometer in the lab and the subsequent values for heart rate, oxygen uptake, power, and cadence are entered into the model as time series variables, and the dynamical systems model then uses a heuristic algorithm to determine individual parameters that best fit the model and predict maximum heart rate and maximal oxygen uptake. The individual parameters are based on an individual's physiology and performance during the test and allow the model to be customized to their performance, removing the need for physiological variables such as age, sex, and body mass, as well as assumptions that all individuals respond the same physiologically to exercise. Based on the preliminary results of this model prediction using dynamical systems, exploring this concept in clinical populations where physiological changes are constantly occurring may provide insight into the prediction capabilities so that in the future, using very little data, such models could predict VO_{2max} with a very high agreement to gold standard CPET without the need for expensive equipment and specialized personnel to run such tests.

The primary purpose of this study was to determine if a dynamical systems model can accurately estimate maximum oxygen uptake from data obtained during a maximal CPET performed on a cycle ergometer in acute myeloid leukemia patients. The secondary purpose was to compare maximum oxygen uptake attained during the CPET, to a non-exercise estimation equation using BMI and body fat percentage. The tertiary purpose was to evaluate if the dynamical system model predicted maximum oxygen uptake was significantly different to the non-exercise estimation equation using BMI or body fat percentage.

Dynamical Systems Model

When compared to the maximum oxygen uptake attained by the patients during the CPET during baseline testing, the dynamical systems model estimation was significantly higher. The maximum oxygen uptake obtained by these patients was categorized as a VO_{2peak} due to their inability to meet the standard criteria for $VO_{2max.}$ These include: a high rate of perceived exertion (>17), a respiratory exchange ratio exceeding 1.1, a blood lactate level greater than 8 mmoles, a plateau of VO_2 even with increasing workloads, or a heart rate within 10 beats per minute of the age-predicated maximum heart rate (Powers, 2012). For rate of perceived exertion, seven patients reported an RPE >17. This is a subjective measurement, and relies on the patient understanding the scale, and also being able to tolerate a maximal level of exertion. These patients were recently diagnosed with leukemia and admitted to the hospital for inpatient treatment, and were all of low physical fitness, therefore, unlikely to be able to tolerate high levels of physical exertion without extreme fatigue. Of the seventeen patients, ten cited leg fatigue as their reason for terminating the test. Only one patient had a plateau of VO_2 with increasing workloads. Three patients had a heart rate within 10 bpm of age-predicted maximum heart rate. Due to the failure to meet these criteria, the highest three values for oxygen uptake during the final minute of the test were averaged to determine $VO_{2peak.}$ Therefore, the VO_2 value achieved by most patients in this study is not believed to be their true physiological max that they could achieve, thus the dynamical system model over-predicting $VO_{2max.}$ The dynamical systems model represents VO_2 as the change in oxygen uptake kinematics in response to the demands placed on the system that disturb the equilibria of the heart rate and $VO_{2.}$ The system has minimum and maximum values, as well as the sub-maximal demand that is a function of exercise intensity. The model is able to recognize that those sub-maximal values experimentally obtained are not the maximal values of the system in the case that a test is terminated early, thus the model over-predicting in some cases (Stirling 2005, Mazzeloni 2016).

Non-Exercise Estimation Equations

The most commonly accepted and widely used equations for predicting VO_{2max} were validated using young, healthy populations and developed for use during steady state exercise. In 2003, Peterson and colleagues examined the efficacy of two of the most commonly used equations, ACSM and Foster, for older, deconditioned adults. They found that the ACSM equation had an overestimation bias for both men and women with the highest overestimation in more fit women. The Foster equation was determined to be appropriate in this population with an R^2=0.7 (Peterson, 2003.) A validity study of non-exercise equations using adult females found that an equation using only one measure of physical activity was just as valid as those with more physical activity questions, but should be used in conjecture with a multivariate regression model using age, gender, and anthropometric data (Cardinal, 1996). In 2005, Jurca et al. performed an analysis of three studies assessing cardiorespiratory fitness using large samples of adult men and women. The National Aeronautics and Space Administration/Johnson Space Center utilized the gold standard maximal exercise test (*n*=1863), Aerobics Center Longitudinal Study (*n*=46,190) utilized a modified maximal test, and the Allied Dunbar National Fitness Survey (*n*=1706), utilized a submaximal test, the non-exercise equations applied to the three populations included age, gender, resting heart rate, and physical activity measurement. The NASA model was most accurate, due to the use of the gold standard VO_{2max} exercise test, but all the estimations were valid in all three populations; NASA r=0.81, ACLS $r^2=0.77$, and ADNF $r^2=0.76$. (Jurca, 2005).

The current study uses a non-exercise equations use age, gender, physical activity, and anthropometric data to predict VO_2 developed by Jackson and Blair (1990). When compared to the VO_{2peak} attained by patients during the CPET, there was no significant difference ($p<.05$) when using BMI as a variable in the equation. However, when using body fat percentage as a variable it was significantly higher. As a general trend, both equations overestimated VO_2 with the exception of a few patients, with the body fat estimation being the highest. Body mass index is a ratio of height to weight, whereas, body fat percentage is a measure of body composition between fat and fat free mass and therefore correlated to physical fitness. Most of these patients experience a loss of body mass as a result of their disease, and changes in body fat percentage may not accurately represent the normal physiology parameter used to develop such equations. The BMI equation may be more appropriate in this population because it is more standardized to exclude individual physiology. These equations have not previously been validated in this population, but may be a viable alternative if other methods for assessing VO_2 are not available. If utilized, BMI should be used as a predictor.

Comparison Between Dynamical Systems Model and Non-exercise Equations

There was no significant difference between VO_{2max} predicted by the dynamical systems model and the non-exercise estimation equations using body fat percentage and BMI. This could be attributed to the overall over-estimation bias of VO_2 for the reasons mentioned previously.

This could also be attributed to the individual variability that was not captured by the paired samples t-tests and will be discussed further in exploratory analysis. The dynamical systems model consistently over-predicted, to what would be assumed to be the true physiological VO_{2max}, whereas the estimation equations over- and under- predicted with large fluctuations between individuals. In this population, non-exercise or mathematical predictions may be better indicators of cardiorespiratory fitness due to their inability to perform maximal cardiorespiratory tests. In the current study, it appears that the dynamical systems model overestimates, it may be more accurate that the CPET obtained value misrepresents their true maximal VO_2 value. The underlying assumption is that the obtained value is their physiological max is violated in this population due to their disease processes and poor physical fitness. The non-exercise equations are more accurate in this population because they account for low physical activity level, age, and body mass index. These patients have very low physical activity levels, are older adults, and have a BMI of (29.3 ± 6.6).

Exploratory Analysis

Due to the individualized nature of the dynamical systems model, exploratory analyses were conducted to capture the inter-variability that was not reflected in the statistical tests ran. The variance between patients and within the sample was not equal, therefore means do not capture the individual differences for each prediction method. For example the dynamical systems model was very accurate with a few patients, and off by as much as 25%. The dynamical systems model had an error of 25.28% (± 27.20), however, the correlation between the model predicted VO_2 values and those obtained during the CPET was, $r(16) = 0.96$ $p < .05$ indicating that the model may produce a more accurate evaluation of VO_{2max} in this cancer population where the CPET performed on the cycle ergometer and due to the disease and treatments may pose a tremendous burden on the patients ability to perform at their best allowing for achievement of maximum oxygen uptake . Examples of time series plots are listed below, in the appendices I and II.

Table 3 presents the percent change between VO_{2peak} attained and predicted VO_{2max} using the dynamical systems model and non-exercise equations including either BMI or percentage body fat. This demonstrates the potential predictive capability of the model in scenarios where a patient's physical limitations to the test are believed to hinder the attainment of a true representation of their cardiorespiratory capacity. Factors such as reduced muscular endurance and strength, lower hemoglobin levels, disease related physical impairments, psychological stress, lack of motivation or energy due to cancer-related fatigue, and unfamiliarity with exercise testing on a cycle ergometer can all contribute to the attainment of lower VO_{2max} during a CPET. The non-exercise estimation equations are designed to assist in the estimation of the patient's cardiopulmonary capacity in scenarios where patients are either unable to perform a CPET, had a percent error of 15.20% ± 39.33 when including BMI, and 26.21% ± 40.75 when including body fat percentage. Table 3 shows how these prediction equations are inconsistent in the direction of error between individuals, while both tending to significantly overestimate with large standard deviations. The reason for these discrepancies between individuals may be due to the tremendous heterogeneity between individuals including different age groups, size, and varied body compositions.

Appendix III contains a line of identity plot of the model predicted VO_{2max} values and the VO_{2peak} values obtained during the CPET. The dynamical systems model predicted VO_2 was within 10% error for seven of the patients (four female, three male). Of those patients, three were the closest to obtaining a VO_{2max} per the criteria with a maximum heart rate within ten beats per minute of their age predicted maximum, and a rate of perceived exertion greater than 17, with one patient reaching a plateau in VO_2 with increasing workloads. Four of the patients within this subgroup cited leg fatigue as their reason for terminating the test. The comorbidities of this group include four patients with arthritis, two with anxiety and depression, one with diabetes, one with COPD. The average age of this subset was 50, BMI of 30.6, and body fat percentage was 29.5. The average test duration was 6.63 minutes with a range of 5-11.36 minutes

A second subset of the patients with the highest percent error between dynamical systems model predicted VO_{2max} and CPET obtained VO_{2peak} consisted of four patients with error of +58%-77%. There were two men and women with the average age of 56, BMI of 29.7, and body fat percentage of 34.9. None of these patients achieved a maximum heart rate within 10 beats per minute of their age predicted max, two had a final RPE of 18, all cited leg fatigue as their reason for terminating the test. The average duration of the test was 5.145 minutes with a range of 2.23-7.5 minutes. The outlier of this subset and the entire population was a 28-year-old male with a BMI of 43.4 and a body fat percentage of 45.6. This patient and one other in this subset had arthritis, two had hypertension.

The patients that the model was most accurate for tended to be women, younger than the average age of the population, with lower body fat percentage and BMI, although the entire population was overweight or obese with the exception of one. The duration of test was associated with more accurate final predictions. Comorbidities did not have an effect on the predictive ability. A longer test would not only provide more data points for the model but would be associated with higher workloads, resulting in higher heart rates and RPE values and higher VO_{2peak} values.

Limitations

Potential limitations for the current study include sample size and generalizability of study results. The exclusion criteria for the EQUAL phase II trial, limited the recruitment of patients who did not have any contra-indication to participate in maximal exercise testing or regular exercise of moderate intensity. Therefore, only patients without any physical limitations besides the potentially altered physiology due to leukemia and treatments participated in the study. However, these results are an important first step in testing the capabilities of the dynamical systems model and further research is needed to continue to explore the accuracy capacity and usability of such model in the oncology setting. Another limitation of the current study is the use of retrospective data, where control over the protocol and variation in the testing parameters could not be manipulated to increase the ability of the dynamical systems model to produce different levels of estimation. For example, if cadence could be altered during testing promoting more pronounced alterations on the physiological response of the patients HR and oxygen uptake during testing, the dynamical systems model could potentially increase its estimation accuracy.

Conclusion

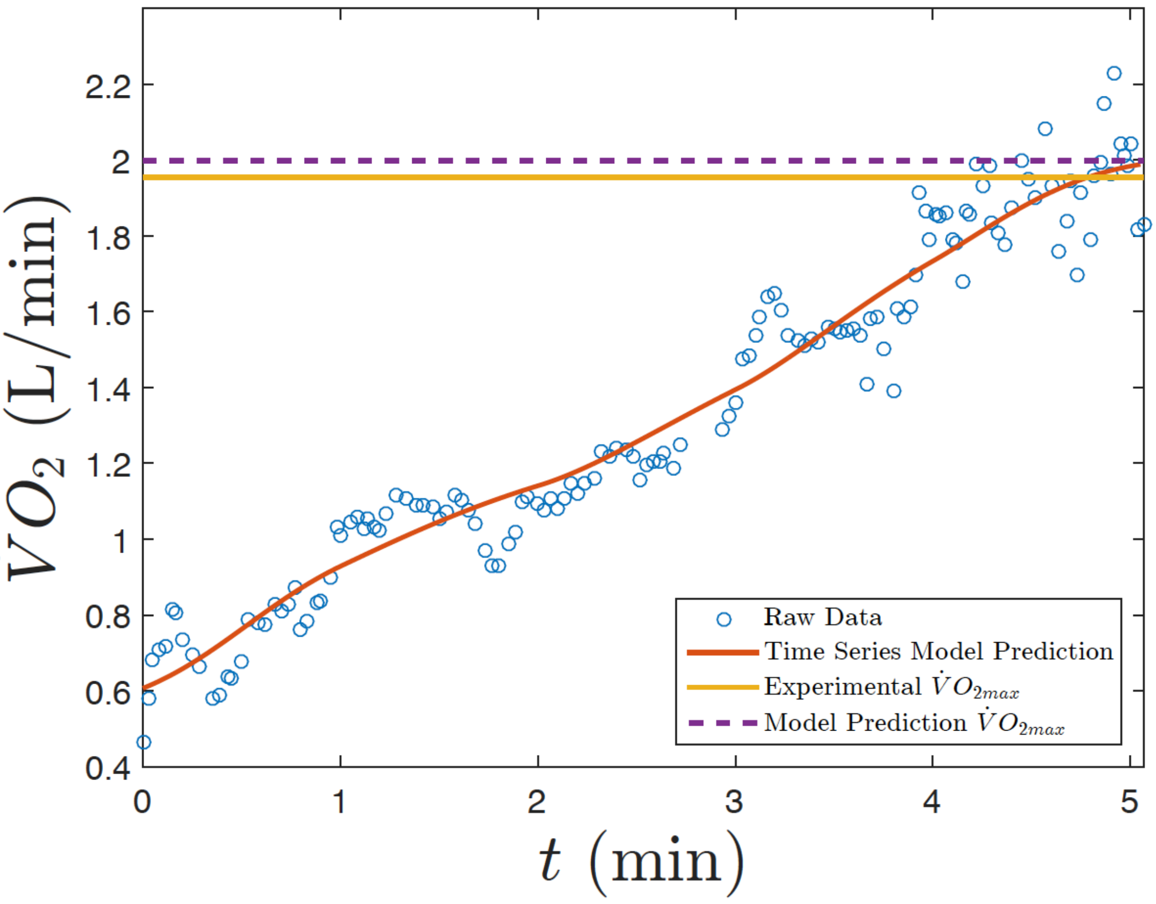
Exercise interventions with adults undergoing inpatient chemotherapy treatment are novel in nature and vary in their implementation. Since exercise has been shown to be safe and feasible to be administered to leukemia patients undergoing treatment, it is important to ensure that exercise intensities are appropriate to alleviate decline or even promote improvements in cardiorespiratory capacity. From a prognostic standpoint, a higher VO_2 value has been associated with better post-transplant outcomes, which could be similar in leukemia patients undergoing treatment. Being able to use parameters such as HR and oxygen uptake to improve the exercise prescription may prove to be an important factor in providing prescriptions that can be more efficacious in promoting most benefits. Based on the results of this preliminary study, the use of a dynamical systems model and/or a non-exercise estimation equation that uses BMI may provide a better overall assessment of the cardiopulmonary capacity of leukemia patients, that is not limited to the physical inability or test specifics that can produce erroneous evaluation of the current cardiorespiratory capacity to be used in the context of an exercise prescription. However, further research must be conducted so better methods for the assessment of cardiorespiratory function can be developed to account for specific physiological alterations in clinical population, that can be captured by the test for a better and more precise assessment be achieved. In conclusion, since transient changes captured in VO_2 in response to the demands placed on the equilibria of the dynamical system, the system is not subject to the same physiological limitations of CPET, potentially providing a more precise VO_{2max} determination. However, this is just speculation at this time since this is just the first study to attempt to investigate the dynamical systems model VO_{2max} predictability in leukemia patients and more research is needed to confirm or refute this possibility.

Recommendations for Future Research

As the first study of it's kind, there are many applications for future research. Exercise prescriptions based on heart rate are difficult in this population due to the variability in their day-to-day heart rate response. More frequent measurements of HR during a submaximal effort would allow for dynamical systems modeling to capture individual differences and fluctuations due to transient responses providing better understanding of HR responses during exercise which could translate in better exercise prescription using HR. The dynamical systems model has been shown in previous studies that it can produce accurate estimations of HR responses with limited data from these CPETs (Mazzoleni et al 2016). The same dynamical systems model may be used for the estimation of VO_{2max} using data from a submaximal effort independent of how different the responses differ between individuals. Using data from a submaximal effort could potentially solve the issue of having to conduct a CPET with indirect calorimetry making it usable in many different setting where such equipment and testing specifics are not possible. Due to the prognostic value of VO_{2max} in oncology, it is recommended that the results of using dynamical systems modeling prediction be tested accounting for reduced physiological capacity of patients (limiting exercise tolerability) which in turn would facilitate the use of estimated VO_{2max} as another tool for physicians to inform best treatment practices in leukemia patients as well as in other cancer populations. Further research is needed to deduce what factors are limiting these patients from achieving higher VO_2 values, and how we can train these individuals to improve their VO_{2max}.

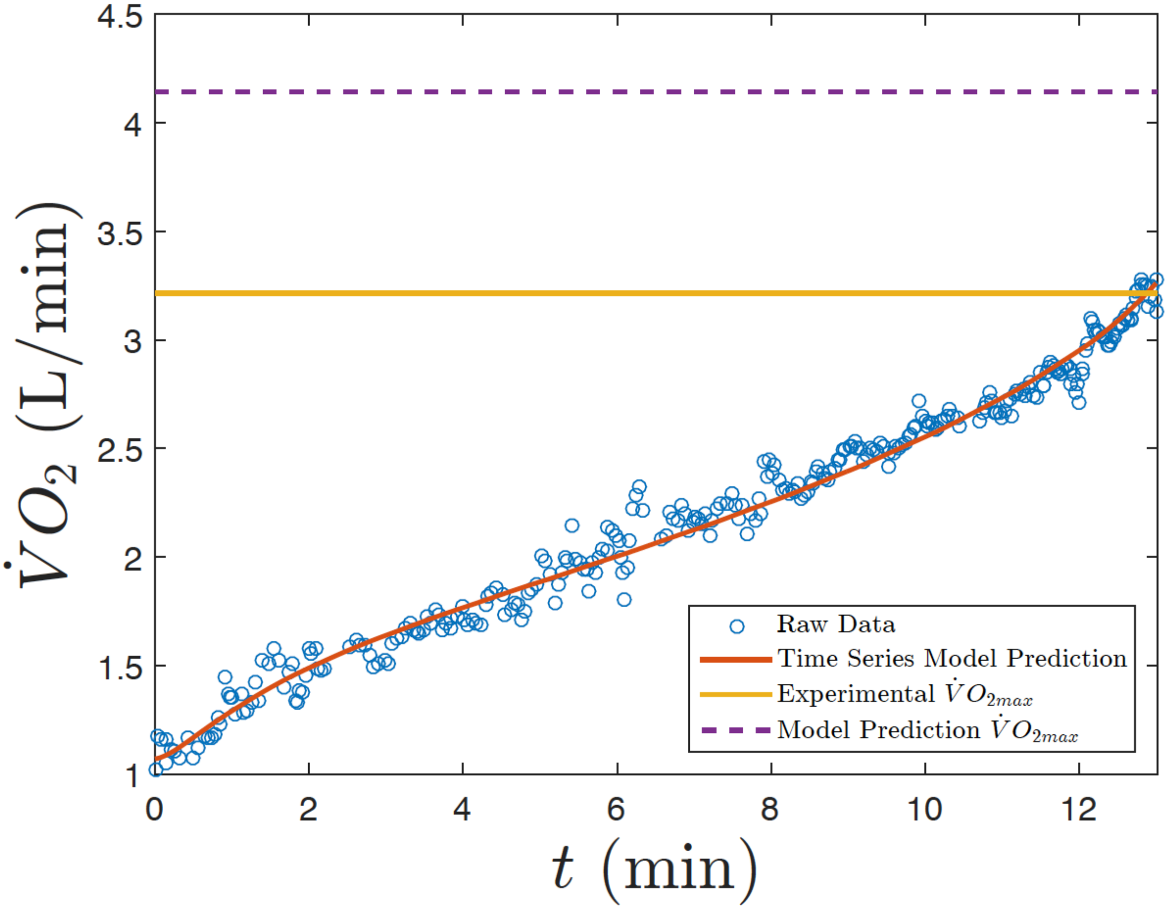
Appendix I

DYNAMICAL SYSTEM TIME SERIES PLOT 2



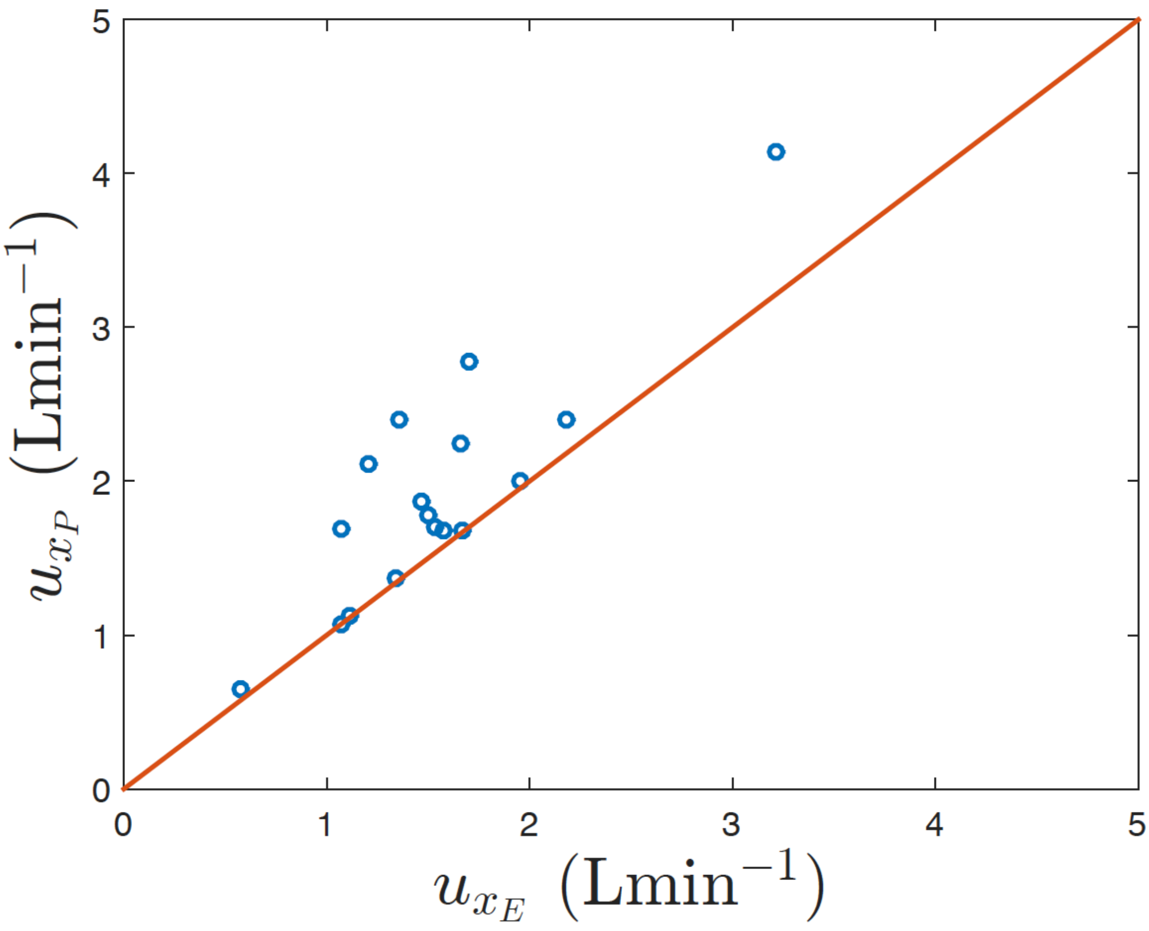
Appendix II

DYNAMICAL SYSTEM TIME SERIES PLOT 2



Appendix III

DYNAMICAL SYSTEM LINE OF IDENTITY PLOT



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