Spring 2017

Repeatability of impedance cardiography in the measurement of cardiovascular hemodynamics during exercise

Lindsey Marie Rodriguez
James Madison University

Repeatability of Impedance Cardiography in the Measurement of Cardiovascular Hemodynamics During Exercise

---

A Project Presented to

The Faculty of the Undergraduate

College of Kinesiology

James Madison University

---

in Partial Fulfillment of the Requirements

for the Degree of Bachelor of Science

---

by Lindsey Rodriguez

April 2017

Accepted by the faculty of the Department of Kinesiology, James Madison University, in partial fulfillment of the requirements for the Degree of Bachelor of Science.

FACULTY COMMITTEE:	HONORS PROGRAM APPROVAL:
Project Advisor: Trent A. Hargens, Ph.D. Date Exercise Science Professor, Kinesiology	Bradley Newcomer, Ph.D. Date Dean, Honors College
Reader: Michael J. Saunders, Ph.D. Date Exercise Science Professor, Kinesiology	
Reader: Christopher J. Womack, Ph.D. Date Exercise Science Professor, Kinesiology	

PUBLIC PRESENTATION

This work is accepted for presentation, in full, at the Kinesiology Student Research Symposium on April 20, 2017 .

Table of Contents

Acknowledgements……iii

List of Tables...……...iv

List of Figures……..v

Abstract……...vi

Chapter I. Introduction……...vii

Chapter II. Methodology……xv

Chapter III. Manuscript……xix

Appendix……..xlii

Bibliography……..liv

Acknowledgements

My senior honors project would not have been possible without the help from project advisor, Dr. Trent A. Hargens. My honors thesis was one of the most challenging projects of my undergraduate career at James Madison University and I am extremely fortunate to have been given the opportunity to work with Dr. Hargens. He guided me through this journey, as well as inspired and encouraged me to complete each piece of this project to the best of my ability. Overall, completing my honors thesis was one the most rewarding experiences thanks to the time and guidance that Dr. Hargens gave me.

I would also like to express my gratitude to Dr. Michael J. Saunders and Dr. Christopher J. Womack for their time and assistance with my research and accepting the responsibility of being the readers of my project. Their advice and encouragement during the writing process greatly aided in the success of my project.

A huge thank you to Daniel Valcicak for working with me every step of the way. I am grateful for your help with data collection, data analysis, and the writing process

Lastly, I would like to thank the kinesiology department at James Madison University for giving me the opportunity to be involved in the kinesiology honors program and conduct this research study. Based on this experience, I feel more prepared and excited to continue conducting research in graduate school.

List of Tables

Table 1. Treadmill Protocol……...xxxii

Table 2. Subject Characteristics……...xxxiii

Table 3A. Mean Values of Primary Hemodynamic Variable for TM1 and TM2……xxxiv

Table 3B. Mean Values of Secondary Hemodynamic Variable for TM1 and TM……xxxv

Table 4A. Primary Intraclass correlations, Standard Errors of Estimate, and Coefficient of Variation for Hemodynamic Variables between TM1 and TM2……..xxxvi

Table 4B. Secondary Intraclass correlations, Standard Errors of Estimate, and Coefficient of Variation for Hemodynamic Variables between TM1 and TM2…….……xxxvii

List of Figures

Figure 1A. Bland-Altman Plot of Moderate Intensity Stage CO..…….xxxviii

Figure 1B. Bland-Altman Plot of Vigorous Intensity Stage CO…….xxxviii

Figure 2A. Bland-Altman Plot of Moderate Intensity Stage SV……..xxxix

Figure 2B. Bland-Altman Plot of Vigorous Intensity Stage SV……...xxxix

Figure 3A. Bland-Altman Plot of Moderate Intensity Stage HR……....xl

Figure 3B. Bland-Altman Plot of Vigorous Intensity Stage HR……xl

Figure 4A. Bland-Altman Plot of Moderate Intensity Stage SVR…….xli

Figure 4B. Bland-Altman Plot of Vigorous Intensity Stage SVR…….xli

Abstract

Repeatability of Impedance Cardiography Hemodynamic Variables During Treadmill Exercise

Purpose To analyze the day to day repeatability of cardiac hemodynamic measurements using a Physio Flow 07 Enduro during treadmill submaximal exercise.

Methods 21 male subject ages 18 and older were studied. Two graded treadmill exercise tests consisting of two 5-minute steady state stages (Moderate and Vigorous intensity) were performed using the PhysioFlow device at least 48 hours apart. Cardiac hemodynamic measurements were compared between stages and trials using repeated measures ANOVA, intraclass correlations, and Bland-Altman plots.

Results Oxygen consumption (VO_2) and respiratory exchange ratio (RER), were not different between the two trials for either Moderate or Vigorous intensities. There was a main effect for intensity for all variables with the exception early diastolic filling ratio (EDFR) and ejection fraction (EF%). Intraclass correlation coefficients between exercise trials were ≥ 0.7 for all hemodynamic variables except for ventricular ejection time (VET) (Moderate and Vigorous Intensity stages), and EDFR (Moderate Intensity Stage). Coefficient of Variation between exercise trials were <12.5% for all hemodynamic variables and <8% for primary hemodynamic variables. Bland-Altman analysis showed good agreement ($P > 0.05$) for all hemodynamic measures except heart rate (HR) ($P = 0.018$ and 0.019 for Moderate Intensity Stage and Vigorous Intensity Stage, respectively), left cardiac work index (LCWi) (Vigorous Intensity Stage, $P = 0.000$), and systemic vascular resistance index (SVRi) (Vigorous Intensity Stage, $P = 0.000$).

Conclusion Measurements from the PhysioFlow was repeatable, with no statistical differences across trials and reasonably strong reliability coefficients for most relevant hemodynamic variables, apart from VET and Low Intensity Stage EDFR, during moderate and vigorous intensity treadmill exercise.

Keywords: PhysioFlow, Impedance Cardiography, hemodynamic variables, cardiac output, stroke volume, non-invasive

Chapter I

Introduction

The study of hemodynamics is a branch of physiology that characterizes the forces and physical aspects that affect the circulation of oxygenated blood. Cardiac output and stroke volume are two critical components of circulation and describe cardiovascular function. Cardiac output measures the amount of blood pumped by the ventricles each minute and is the primary indicator of the functional capacity of the circulation to meet the increased demands during physical activity. Cardiac output, the product of stroke volume and heart rate, is also one of the most basic means for assessing cardiac function and hemodynamics (Pickett, 1992). A healthy heart will pump 4-8 liters of blood per minute at rest. Untrained individuals have an average maximum cardiac output of 14 to 20 L/min and extremely trained individuals can reach measurements of up to 40 L/min (Powers, 2014). When an individual is resting they have an average heart rate of 60-100bpm. Resting stroke volume is 60-100 milliliters per beat on average, however it is possible that all of these hemodynamic measurements will vary based on the training level of an individual (Powers, 2014). Changes in stroke volume, heart rate and other factors influencing cardiac output vary considerably during exercise and under different health and disease conditions; therefore accurate measurements of cardiac output and stroke volume are very important for both clinical and exercise purposes (Charloux, 2000).

Hemodynamic measurements are commonly used for clinical purposes and contribute to the understanding of the pathophysiology behind diseases. These measurements are also applicable in high-risk patients undergoing surgery as well as critically ill, medically treated patients. Hemodynamic measurements, such as cardiac output and stroke volume can accurately determine heart function, and measure the continuously changing function of the heart as related

to the process of a disease. These measurements can guide treatments and interventions based on a rational physiologic source, therefore aiding in the prognosis and therapy plans for patients (Swan, 1983).

Hemodynamic measurements are also important in exercise physiology research and exercise testing. Results can be used for multiple purposes such as exercise prescription and clinical diagnosis. Jennings et al (1986) used hemodynamic measurements during exercise to assess the effect of changes in physical activity on major cardiovascular risk factors, hemodynamics, sympathetic function, and glucose utilization in men. An indirect Fick method and mixed venous partial pressure of carbon dioxide (pCO_2) by a carbon dioxide rebreathing method were used to measure cardiac output. By studying hemodynamics and other factors during exercise, this study found that increasing physical activity in young sedentary normal adults would decrease risk of a chance for subsequent development of cardiovascular disease (Jennings, 1986).

Previous techniques for measuring hemodynamic principles are complicated, invasive, and typically require trained personnel. As a result, they are highly impractical. The criterion technique developed for measuring cardiac output is known as the Fick Method. This method determines cardiac output from the direct measurements of oxygen content of arterial and mixed venous blood as well as measurements of oxygen consumption (VO_2). This technique was first utilized in 1940 to determine the cardiac output of a man before and after a blood transfusion surgery (Laszlo, 2004). The Fick method requires that arterial blood samples from the arterial line and mixed venous blood samples from the distal pulmonary arterial opening are obtained simultaneously using a catheter. From this sample partial pressure of oxygen (pO_2), partial pressure of carbon dioxide (pCO_2), pH, and base excess can be determined. Arterial and mixed

venous oxygen consumptions are then calculated as the product of hemoglobin, the hemoglobin-binding constant of oxygen (1.34g/L), and oxygen saturation because most of the oxygen in arterial blood is bound to hemoglobin. Oxygen consumption (VO_2) and the amount of carbon dioxide exhaled (VCO_2) are measured by a breath-by-breath analysis (Hoeper, 1999). Cardiac output (Q) is then calculated according to the formula:

$$Q=VO_2/(CaO_2-CvO_2)$$

In this equation, VO_2 represent oxygen consumption, CaO_2 is the measured oxygen concentration of arterial blood, and CvO_2 is the measured oxygen concentration of mixed venous blood.

Because this technique requires catheterization of the pulmonary arterial circulation, it is highly invasive for the individual. The indirect Fick method uses an estimated value for mixed venous gas pressure and blood-gas contents, which are derived from known partial pressures of the gas in the blood (Laszlo, 2004). The accepted standard for measuring cardiac output was considered the direct Fick method until other hemodynamic monitoring methods were later developed. Another strategy is the dye dilution technique. For this technique, cardiac output is measured by rapidly injecting a known amount of dye into one site of the circulatory system and withdrawing blood at the distal end of the system. This method uses an equation to calculate cardiac output, which is defined by dividing the indicated amount of an injected dye by the area under the dilution curve measured downstream (Lund- Johansen, 1990). Studies found that the dye dilution technique is just as reliable as the Fick method and it was later noted this dye dilution method could also be used during exercise (Taylor, 1966; Lund- Johansen, 1990). In 1953, heat was used as a substitute for dye indicator for a new thermodilution technique. A solution that is colder than the blood in circulation is injected intravenously and thermocouples

are placed in the right ventricle and thoracic aorta record temperature changes in the blood (Fegler, 1957). The cardiac output can then be calculated from the thermodilution curves.

The invention of the right heart catheterization also known as the Swan-Ganz catheter, significantly influenced the development of cardiac output monitoring. The most trusted method for hemodynamic measurements and clinical diagnostic purposes has been the invasive pulmonary artery catheterization-based thermodilution technique and is typically used as comparison for new hemodynamic monitoring devices (Borlaug, 2009; Pugsley, 2010). However, this technique holds many possible risks. It does not allow the individual to move or exercise and may even require a hospital stay (Jones, 2011). Therefore, non-invasive techniques could greatly enhance the ability to measure these hemodynamic variables.

The most practical non-invasive methods for measuring cardiac output are Doppler echocardiography, partial rebreathing indirect Fick method, and impedance cardiography; however their accuracy and repeatability during exercise is still uncertain (Charloux, 2000). During the Doppler echocardiography method, the aortic diameter is measured using a pulsed ultrasound. A continuous-wave Doppler ultrasound is used to obtain the aortic blood velocity (Huntsman, 1983). Cardiac output can be calculated through the measurement of aortic blood velocity without requiring aortic size measurements (Haites, 1985). It was found that this technique is reliable when used during submaximal and peak exercise (Shaw, 1985). A study comparing the Doppler ultrasound method and the thermodilution catheterization method found that the assessment of cardiac output via non-invasive techniques compared to cardiac output measurements using invasive catheterization techniques were entirely consistent with previous published work, which showed validity (Huntsman, 1983).

The partial rebreathing technique uses a differentiated form of the Fick equation to calculate cardiac output. Changes in carbon dioxide (CO_2) removal and partial pressure of end-tidal CO_2 measurements as a result of partial rebreathing are used to estimate the measurement for the pulmonary capillary blood flow. It is assumed that the mixed venous CO_2 content does not change during a brief change in ventilation. Oxygen saturation and inspired oxygen concentration measurements are then incorporated into the equation to calculate the total cardiac output (Haryadi, 2000).

Impedance cardiography has been advancing for over 40 years and has been used to monitor overall cardiac function. The original impedance design consisted of a configuration of four band electrodes with two electrodes placed around the neck and two placed on around the abdomen. One inner electrode is place around the base of the neck and the other is between the xiphoid process and sternum. The inner electrodes are the sensing electrodes and pick up the signals put out by the outer electrodes. The outer electrodes are placed at least three centimeters outside the inner electrodes in order to obtain proper readings and conduct a small current. This continuous current is conducted through the chest electrodes starting from the top outer neck electrode. A voltage drop is generated between the inner neck electrode and the inner abdomen electrode. This voltage is recognized by the impedance amplifiers, which obtain a value for the magnitude of the impedance in ohms. The value can then be derived to calculate ventricular stroke volume and cardiac output. The stroke volume equation is:

$$SV= p\ (L/Z_0)^2\ (dZ/dt\ max)\ (LVET)$$

In this equation, the resistivity of blood in ohms is represented by p (ohms), L (cm) is the distance between the neck inner sensing electrode and the abdominal inner sensing electrode, Z_0 (ohms) represents the average body impedance between the neck inner electrode and the

abdominal inner electrode, dZ/dt (ohms/second) the first derivative of change in impedance in the thorax region, and LVET (sec) represents the time it takes for the left ventricle to eject its blood during systole (Kubicek, 1970). Multiple research studies have been performed using alterations to the basic concept of impedance for measuring cardiac output and other hemodynamic measurements for both exercise and clinical purposes.

A newer model of impedance cardiography called PhysioFlow uses a modified equation to calculate hemodynamic measurements. This device is based on the equation:

$$CO=fc * SV\ index * BSA$$

In this equation, fc is the heart rate in beats per minute, BSA is the body surface area in meters squared and is calculated according to the Haycock formula (BSA=0.024265 x body mass in $kg^{0.5378}$ x Height in $cm^{0.3964}$). SV index is measured in ml/m^2 and is determined by dividing the stroke volume by the surface area of the body (Charloux, 2000). The PhysioFlow device is designed to have enhanced signaling, making it capable to provide better data processing. A study comparing measurements of cardiac output during submaximal exercise in healthy adults using the PhysioFlow device and the direct Fick method found high correlation between these two methods and accurate measurements of cardiac output using the new impedance PhysioFlow device. Cardiac output was recorded at rest and during cycle exercise at 10 to 50Watts. The PhysioFlow cardiac output measurements were from 4.34 to 14.841L/min and the Direct Fick method had cardiac output measurements of 3.60-15.03 L/min (Charloux, 2000).

A subsequent study tested the reproducibility and accuracy of the PhysioFlow device in moderately trained, healthy subjects performing identical graded maximal exercise tests on an electronically braked bicycle ergometer on two separate occasions, three days apart. In a subgroup of seven subjects, cardiac output was measured using the direct Fick method in parallel

with the PhysioFlow to test for accuracy and concluded that the PhysioFlow can produce clinically accurate measurements during incremental maximal exercise (Richard, 2001). A different study compared PhysioFlow cardiac output measurements during different exercise intensities to the CO2 rebreathing technique. There were no significant differences with the PhysioFlow cardiac output measurement and the CO2 rebreathing cardiac output measurements during mild to high intensity steady-state exercises on a cycle ergometer (Tordi, 2004). Another study aimed to assess the reproducibility of cardiac output and hemodynamic parameters from impedance cardiography via PhysioFlow during resting positions of supine, seating and standing and during light to moderate steady-state exercise on a cycle ergometer. Both resting and exercise positions had an intraclass correlation coefficient (ICC) $\geq$ 0.7 for all variables (Schulz, 2012). Based on previous research, it is apparent that the PhysioFlow makes measuring CO and other hemodynamic factors during exercise easier, however the repeatability of this device during other modes of exercise, including treadmill exercise, is still unknown.

The purpose of this study was to analyze day to day repeatability of cardiac hemodynamic measurements using a PhysioFlow device (PhysioFlow 07 Enduro) during submaximal treadmill exercise. Due to the research on the accuracy of this equipment, it was hypothesized that the PhysioFlow measurements would demonstrate good consistency between repeated submaximal treadmill exercise. If this device proves to be repeatable, it has potential to be a new non-invasive standard for hemodynamic measuring during both exercise and clinical situations.

Chapter II

Methodology

Subjects:

The study aimed to obtain a sample of 15 to 30 male students from James Madison University and the Harrisonburg community who were 18 years or older. Recruitment of subject was via JMU bulk email requests and through word-of-mouth. Individuals with previous diagnosis of cardiovascular, pulmonary, or metabolic disease, as well as individuals who are not capable of vigorous exercise intensity due to an orthopedic limitation were excluded from participation. Individuals taking medications that impact cardiovascular hemodynamics were omitted. All procedures were approved by the Institutional Review Board (IRB).

Pre-test

Following completion of a signed informed consent form, subjects were asked to complete two questionnaires, which were sent via online links. The first questionnaire, the Physical Activity Readiness Questionnaire (PARQ), is a short 7-question assessment to identify reasons the individual should not participate in moderate-to-vigorous exercise (Pescatello, 2014). The second questionnaire is the International Physical Activity Questionnaire Short Form (IPAQ). This is a validated questionnaire to assess physical activity levels in a subjective manner (Ekelund, 2006).

Testing Procedure:

After completing necessary paperwork, the subject's height and weight were measured. Weight measurements were recorded to the nearest 0.1kg using a physician's scale and height was measured and recorded to the nearest 0.5cm using a wall stabilized stadiometer. The subject was then prepped for the PhysioFlow device by shaving and/or cleaning the electrode placement

sites in order to prevent interference. A resting blood pressure measurement was obtained prior to exercise using a stethoscope and blood pressure cuff. Blood pressure procedures followed ACSM procedures describes in the ACSM's Guidelines for Exercise Testing and Prescription (Pescatello, 2014).

The subjects then completed a maximal graded exercise test on the treadmill utilizing a standardized ramped protocol developed specifically for this study. The test began with a one minute walking stage at 2.6 mph and 0% grade (3 METs) and progressed to a second one minute walking stage at 3.1 mph and 1.5% grade (4 METs). The subject then entered their first five minute- modereate intensity steady state stage at 3.6 mph and 2.5% (5 METs). Three minutes into this stage blood pressure was measured and entered into the PhysioFlow software. After this five minute stage, the subjects entered a one minute stage at 4 mph and 3.5% grade (6 METs). They then entered their second five minute-vigorous intensity steady state stage at 4mph and 5.5% grade (7 METs). Another blood pressure measurement was taken and recorded three minutes into this stage. At the end of the second five-minute stage, speed and/or grade increased each minute until the subject reached voluntary fatigue, could no longer physically continue, or experienced adverse signs or symptoms. Oxygen consumption (VO_2) was measured continuously throughout the test with a metabolic cart (Parvo Medics TrueOne 2400) indirect calorimetry system. After the initial maximal graded exercise test, subjects were asked to return to the human performance lab on a subsequent day after a minimum two day recovery period. Testing was conducted at the same time of day in order to eliminate any diurnal influence on hemodynamic measures. On the subsequent testing date a second maximal treadmill test was conducted, using the same procedure described above.

Hemodynamic Measurement

A PhysioFlow 07 Enduro (impedance cardiography device) was used to monitor hemodynamic measurements. These measurements include stroke volume (mL), stroke volume index (mL/m^2), heart rate (bpm), cardiac output (L/min), cardiac output index (L/min/m^2), contractility index, ventricular ejection time (ms), end diastolic filling ratio (%), left cardiac work index (kg·m/m^2), systemic vascular resistance (dyn.s/cm5), systemic vascular resistance index (dyn·s/cm5·m^2), end diastolic volume est (mL), ejection fraction est (%), mean arterial pressure (mmHg) and rate pressure product (mmHg·bpm).

Heart rate (HR) measures the amount of times the heart beats per minute. Stroke volume index (SVi) divides the stroke volume (SV) value, which is the amount of blood pumped per beat, corrected for body surface area. Similarly, Cardiac output (CO) measures the volume of blood pumped by the heart each minute, and cardiac output index (COi) divides this values by the body surface area. Left cardiac work index (LCWi) represents the amount of work the left ventricle must perform each minute in order to pump the blood out to the aorta and is normalized for the individual body surface area. Systemic vascular resistance (SVR) is the resistances to blood flow from all of the systemic vasculature, and systemic vascular resistance index (SVRi) is the measurement relative to the individual's body surface area. End diastolic volume (EDV) is the amount of blood in the ventricles just prior to systole. Contractility index (Ci) represents the contractile ability of the heart. Early diastolic filling ratio (EDFR) is the ratio of early to late ventricular filling velocities and can determine the functional ability of the left ventricle of the heart. Ventricular ejection time (VET) measures the time it takes for the left ventricle to pump blood in one beat and ejection fraction (EF) is the percentage of blood leaving the heart in one pump. Mean arterial pressure (MAP) represents the "afterload" or the pressure that the left

ventricle must exceed in order to pump blood out of the aorta. Rate pressure product (RPP) measures the workload of the heart.

Analysis:

Repeated measures ANOVA, intraclass correlations, and Bland-Altman plots were employed to determine mean differences, agreement and repeatability of the hemodynamic variables at the two absolute submaximal intensities.

Timeline:

Recruitment of subjects began in April 2016. The recruitment continued throughout November 2016 until a total of 21 college aged male subjects completed the study. Each subject reported to the Human Performance Lab on the campus of James Madison University to complete the study protocol. The completion date for data collection was April 2017.

Chapter III

Manuscript

Repeatability of Impedance Cardiography Hemodynamic Variables During Treadmill Exercise

Abstract

Purpose To analyze the day to day repeatability of cardiac hemodynamic measurements using a Physio Flow 07 Enduro during treadmill submaximal exercise.

Methods 21 male subjects, ages 21.4 ± 0.5 were studied. Two graded treadmill exercise tests consisting of two 5-minute steady state stages (Moderate and Vigorous intensity) were performed using the PhysioFlow device at least 48 hours apart. Cardiac hemodynamic measurements were compared between stages and trials using repeated measures ANOVA, intraclass correlations, and Bland-Altman plots.

Results Oxygen consumption (VO_2) or respiratory exchange ratio (RER), obtained from the Parvo Medics TrueOne 2400, were not different between the two trials for either Moderate or Vigorous intensity steady-state stage. There was a main effect for intensity for all variables with the exception early diastolic filling ratio (EDFR) and ejection fraction (EF%). Intraclass correlation coefficients between exercise trials were ≥ 0.7 for all hemodynamic variables except for ventricular ejection time (VET) (Moderate and Vigorous Intensity stages), and EDFR (Moderate Intensity Stage). Coefficient of Variation between exercise trials were <12.5% for all hemodynamic variables and <8% for primary hemodynamic variables. Bland-Altman analysis showed good agreement ($P > 0.05$) for all hemodynamic measures except heart rate (HR) ($P = 0.018$ and 0.019 for Moderate Intensity Stage and Vigorous Intensity Stage, respectively), left cardiac work index (LCWi) (Vigorous Intensity Stage, $P = 0.000$), and systemic vascular resistance index (SVRi) (Vigorous Intensity Stage, $P = 0.000$).

Conclusion Measurements from the PhysioFlow was repeatable, with no statistical differences across trials and reasonably strong reliability coefficients for most relevant hemodynamic variables, apart from VET and Low Intensity Stage EDFR, during moderate and vigorous intensity treadmill exercise.

Keywords: PhysioFlow, Impedance Cardiography, hemodynamic variables, cardiac output, stroke volume, non-invasive

Introduction

Changes in stroke volume (SV), heart rate (HR) and other hemodynamic factors influencing cardiac output (CO) vary considerably during exercise and under different health and disease conditions; therefore accurate measurements of cardiac output and stroke volume are very important for both clinical and exercise purposes (Charloux, 2000). The Fick Method, a criterion technique for assessing these variables, requires arterial blood samples and is therefore an invasive procedure (Hoeper, 1999). Thus, accurate and reliable methods for non-invasively determining hemodynamic variables would be of practical significance.

The most practical non-invasive methods for measuring CO are Doppler echocardiography, partial rebreathing indirect Fick method, and impedance cardiography; however their accuracy and repeatability during exercise is still uncertain (Charloux, 2000). It was found that the Doppler echocardiography technique is reliable when used during submaximal and peak exercise (Shaw, 1985). The partial rebreathing technique uses changes in carbon dioxide (CO_2) removal and partial pressure of end-tidal CO_2 measurements as a result of partial rebreathing to estimate the measurement for the pulmonary capillary blood flow. Oxygen saturation and inspired oxygen concentration measurements are then incorporated into the equation to calculate the total cardiac output (Haryadi, 2000).

Impedance cardiography is a noninvasive technology that measures the total electrical conductivity of the thorax and its changes in time to process cardiodynamic parameters. Day to day variations in physiology can also influence impedance cardiography by +/- 4.6% for CO and +/- 6.1% for SV (Ng, 1991). More recently, a newer model of impedance cardiography, called PhysioFlow, has been designed to have enhanced signaling, making it capable to provide better data processing. A study comparing measurements of CO during submaximal exercise in

healthy adults using the PhysioFlow device and the direct Fick method found high correlation between these two methods and accurate measurements of CO during cycle exercise using the new impedance PhysioFlow device (Charloux, 2000). A subsequent study tested the reproducibility and accuracy of the PhysioFlow device in moderately trained, healthy subject performing identical graded maximal exercise tests on a cycle ergometer on two separate occasions, three days apart. In a subgroup of seven subjects, cardiac output was measured using the direct Fick method in parallel with the PhysioFlow to test for accuracy and concluded that the PhysioFlow can produce clinically accurate measurements during incremental maximal exercise on a bicycle (Richard, 2001). Furthermore, a prior study found no significant differences between PhysioFlow CO measurement and the CO2 rebreathing cardiac output measurements during mild to high intensity steady-state exercises on a cycle ergometer (Tordi, 2004). Another study observed intraclass correlation coefficients (ICC) $\geq$ 0.7 for several hemodynamic variables for repeated PhysioFlow measurements during resting positions of supine, seated and standing and during light to moderate steady-state exercise on a cycle ergometer. (Schulz, 2012). Based on previous research, it is apparent that the PhysioFlow makes measuring CO and other hemodynamic factors during cycle ergometer exercise easier, however the repeatability of this device during other modes of exercise, including treadmill exercise, has not been explored.

The purpose of this study was to analyze day to day repeatability of cardiac hemodynamic measurements using a PhysioFlow device (PhysioFlow 07 Enduro) during submaximal treadmill exercise. It was hypothesized that the PhysioFlow measurements would demonstrate good consistency between repeated submaximal treadmill trials.

Materials and Methods

Subjects:

21 male students ages 21.4 ± 0.5 were recruited from James Madison University and the Harrisonburg community via email and word of mouth. Individuals with previous diagnosis of cardiovascular, pulmonary, or metabolic disease, as well as individuals who are not capable of vigorous exercise intensity due to an orthopedic limitation were excluded from participation. Individuals taking medications that impact cardiovascular hemodynamics were also omitted. Procedures were approved by the Institutional Review Board (IRB).

Testing Procedure:

Subjects completed a maximal graded exercise test on the treadmill utilizing a standardized ramping protocol developed specifically for this study (Table 1). The test began with a one minute walking stage at 3 METs and progressed to a second one minute walking stage at 4 METs. The subject then entered a five minute- Moderate Intensity steady state stage at 5 METs. Three minutes into this stage, blood pressure was measured and entered into the PhysioFlow software. After this five-minute stage (Moderate Intensity Stage), the subjects completed a one-minute stage at 6 METs, followed by a five minute-Vigorous intensity steady state stage (Vigorous Intensity Stage) at 7 METs. Another blood pressure measurement was taken and recorded three minutes into this stage. At the end of the second five-minute stage, speed and/or grade increased each minute until the subject reached voluntary fatigue, could no longer physically continue, or experienced adverse signs or symptoms, in order to quantify their VO_2 Max. Oxygen consumption was measured continuously throughout the test with a breath-by-breath (TrueOne 2400, Parvo Medics, Sandy, UT) indirect calorimetry system. After the initial graded exercise test, subjects were asked to return to the human performance lab on a

subsequent day after a two day recovery period. Testing was conducted at the same time of day in order to eliminate any diurnal influence on hemodynamic measures. On the subsequent testing date, a second maximal treadmill test was conducted using the same procedure described above.

Hemodynamic Measurement

A PhysioFlow 07 Enduro (impedance cardiography device) was used to monitor hemodynamic measurements. These measurements included stroke volume (SV), stroke volume index (SVi), heart rate (HR), cardiac output (CO), cardiac output index (COi), contractility index, ventricular ejection time (VET), early diastolic filling ratio (EDFR), left cardiac work index (LCWi), systemic vascular resistance (SVR), systemic vascular resistance index (SVRi), end diastolic volume (EDV), ejection fraction (EF), mean arterial pressure (MAP) and rate pressure product (RRP).

Analysis:

Repeated measures ANOVA, intraclass correlations, and Bland-Altman plots were employed to determine mean differences, agreement and repeatability of the hemodynamic variables at the two steady state submaximal intensities. All statistical analyses were carried out using SPSS Statistical Package version 24.0 (IBM Corp., Armonk, NY). Statistical significance was set *a priori* at $P < 0.05$.

Results

Subject characteristics are in Table 1. As expected, VO_2 and RER increased during the two exercise trials as the intensity increased, but there was no statistical difference in VO_2 or RER between the two trials for either moderate or vigorous steady-state stages. For the PhysioFlow derived hemodynamic variables, there was a main effect for intensity for all variables with the exception EDFR (significant interaction for intensity and trial, $P = 0.013$) and

EF% (no significant main effects). For HR, there was a significant main effect for trial (P = 0.013), with Trial 1 heart rates significantly higher for both stages. For all other hemodynamic variables, there was no statistical difference between exercise trials. Mean values for hemodynamic and exercise variables can be found in Table 3.

Intraclass correlation coefficients between exercise trials were $\geq$ 0.7for all hemodynamic variables except for VET (both stages), and EDFR (Moderate Intensity Stage). Table 4 presents Intraclass correlation coefficient, standard errors of the estimate, and coefficient of variation. Coefficient of Variations were <12.5% for all hemodynamic measurements and <8% for all primary hemodynamic measurements (Table 4). Bland-Altman analysis showed good agreement (P >0.05) for all hemodynamic measures except HR (P = 0.018 and 0.019 for Moderate Intensity Stage and Vigorous Intensity Stage, respectively), LCWi (Vigorous Intensity Stage, P = 0.000), and SVRi (Vigorous Intensity Stage, P = 0.000). Figures 1-4 display Bland-Altman plots for CO, SV, HR, and SVR.

Discussion

This study was designed to test the repeatability of measurements obtained from PhysioFlow impedance cardiography during moderate and vigorous treadmill exercise. Overall, it appears that the PhysioFlow demonstrated good consistency for most hemodynamic measurements during treadmill exercise, with the exception of EDFR and VET, when considering mean differences and ICC data. There was no significant difference in VO_2 or RER between the two trials for either stage, indicating that the subjects exercised as the same workload on both days. There was an increase in VO_2, SV, HR, CO, CI, EDV, CTi, VET, and LCWi with increased intensity, which was to be expected. The only variables that did not increase as intensity increased for were EDFR and EF%. For TM1, there was no statistical

difference in CTi, BP, or ESV between Moderate Intensity Stage and Vigorous Intensity stage, therefore EDFR did not increase. For TM2, there was a statistical difference in CTi between stages, no statistical difference in BP, and no statistical difference in ESV. It is expected to see an increase in EDFR for TM2 based off the proposed mechanisms, therefore a possible explanation could be device error (Sengupta, 2008).

In a previous study, Charloux found the PhysioFlow device to be reliable at rest and during cycle exercise at 10 to 50 Watts by comparing this device to the Direct Fick Method using catheterization (Charloux, 2000). Another study found the PhysioFlow to produce clinically accurate measurements during incremental, maximal cycle exercise (Richard, 2001). Schultz validated the PhysioFlow during supine, seated and standing positions with intraclass correlation coefficient ≥ 0.7 for all hemodynamic variables in each posture, as well as each intensity of exercise. Shultz's study also showed reliable measurements during light to moderate steady-state exercise on a cycle ergometer (Shultz, 2012). The present study is the first to investigate the PhysioFlow's reproducibility in incremental and steady-state treadmill exercise.

The aforementioned study from Richard evaluated the reproducibility of the device using an incremental, maximal cycle test. This is different from the present study, which used the final two minutes of a five minute steady state stage. Overall, Richard's results produced clinically accurate measurements, as validated by comparing to the Direct Fick method, and had a reliability coefficient of $r=0.95$ for CO on different days and a validity coefficient of $r=0.94$ (Richard, 2001). Shultz examined measurements obtained for five minutes once the subject reached steady state with first minute of steady state data used for analysis. The authors reported that all ICC's were above 0.7 for each variable at each intensity of cycle exercise, which were similar intensities to that of the present study (Shultz, 2012).

The present study found that TM1 HR was significantly higher than TM2 HR, however, post hoc analysis showed no statistical difference in HR across trials with a given intensity. It is not ncommon for there to be a significant difference in HR between trials. A study comparing test-retest HR of males during rest, treadmill and cycle exercise found a statistical difference in about one-third of the pair comparisons. This group's mean heart rate during exercise was significantly lower on any successive test, compared to the week prior and was noted to be lower at all levels of submaximal exercise during the successive test. It was suggested that the decrease in HR may have been due to familiarity with the setting and the task (Sime, 1972).

An ICC of $r \geq 0.7$ was achieved for all hemodynamic variables except VET and Moderate Intensity Stage EDFR. It is likely that the difference in HR between TM1 and TM2 could be the reason for the lack of agreement in VET, because HR is inversely related to VET (Vanfraechem, 1979; Weissler 1961). Factors such as end systolic volume (ESV), contractility, and afterload, which are estimated from diastolic blood pressure (DBP), influence EDFR (Courtois, 1992; Moon, 1994). When the heart contracts, the left ventricle twists as it pumps blood through the aorta. During diastole, the heart muscles relax and the ventricle untwists, creating a suction gradient, which results in early diastolic filling. Greater contractility will produce lower ESV, which increases the suction gradient even more, as long as the afterload remains low (Sengupta, 2008; Courtois, 1992). The present study did not find evidence of statistical difference in ESV, CTi, or DBP that would suggest a lack of agreement between the two trials. It is possible that there may be a day-to-day variation in EDFR causing the low reliability coefficient, however future research is needed to confirm.

A limitation in this study was that the subjects in the sample were recruited via word-of-mouth and bulk-email requests and therefore the sample was not completely random. The

repeatability of the PhysioFlow is supported by the results of previous researchers. However, the present study cannot validate this device due to lack of access to direct measurements. A larger, more diverse sample, as well as, comparing the PhysioFlow measurements to the Direct Fick method could have yielded more comprehensive results.

In the future, researchers may wish to investigate the repeatability of the PhysioFlow across different modes of exercise, such as cycle and treadmill, as well as using invasive methods to validate their results. Overall, this study found that the PhysioFlow device was fairly repeatable with no statistical differences across trials and moderately strong reliability coefficients for most relevant hemodynamic variables, apart from VET and Moderate Intensity Stage EDFR, during moderate and vigorous intensity treadmill exercise.

Manuscript References

1. Charloux, A., Lonsdorfer-Wolf, E., Richard, R., Lampert, E., Oswald-Mammosser, M., Mettauer, B., & Lonsdorfer, J. (2000). A new impedance cardiograph device for the non-invasive evaluation of cardiac output at rest and during exercise: comparison with the "direct" Fick method. *European journal of applied physiology,* 82(4), 313-320.
2. Courtois, M., Mechem, C. J., Barzilai, B., & Ludbrook, P. A. (1992). Factors related to end-systolic volume are important determinants of peak early diastolic transmitral flow velocity. *Circulation*, *85*(3), 1132-1138.
3. Ekelund, U., Sepp, H., Brage, S., Becker, w., Jakes, R., Hennings, M., & Wareham, N. J. (2006). Criterion-related validity of the last 7-day, short form of the International Physical Activity Questionnaire in Swedish adults. *Public health nutrition,* 9(02), 258-265.
4. Haryadi, D. G., Orr, J. A., Kuck, K., McJames, S., & Westenskow, D. R (2000). Partial CO2 rebreathing indirect Fick technique for non-invasive measurement of cardiac output. *Journal of clinical monitoring and computing,* 16(5-6), 361-374.
5. Hoeper, M. M., Maier, R., Tonger, J., Niedermeyer, J., Hohlfeld, J. M., Hamm, M. & FAbel, H. (1999). Determination of cardiac output by the Fick method, theremodilution, and acetylene rebreathing in pulmonary hypertension. *American Journal of Respirtatory and Critical Care Medicine,* 160(2). 535-541.
6. Kubicek, W. G., Patterson, R. P., & Witsoe, D. A. (1970). Impedance cardiography as a noninvasive method of monitoring cardiac function and other parameters of the cardiovascular system. *Annals of the New York Academy of Sciences,* 170(2), 724-732.

7. Lund-Johansen, P. (1990). The dye dilution method for measurement of cardiac output. *European heart journal,* 11(suppl 1), 6-12.

8. Ng, H. W., Walley, T., Tsao, Y., & Breckenridge, A. M. (1991). Comparison and reproducibility of transthoracic bioimpedance and dual beam Doppler ultrasound measurement of cardiac function in healthy volunteers. *British journal of clinical pharmacology*, *32*(3), 275-282.

9. Moon, M. R., Ingels, N. B., Daughters, G. T., Stinson, E. B., Hansen, D. E., & Miller, D. C. (1994). Alterations in left ventricular twist mechanics with inotropic stimulation and volume loading in human subjects. *Circulation*, *89*(1), 142-150.

10. Pescatello L. S., and American College of Sports Medicine. (2014). *ACSM's Guidelines for Exercise Testing and Presciption (9th edition.).* Baltimore, MD: Wolters Kluwer/Lippincott Williams & Wilkins Health.

11. Richard, R., Lonsdorfer-Wolf, E., Charloux, A., Doutreleau, S., Buchheit, M., Oswald-Mammosser, M., ... & Lonsdorfer, J. (2001). Non-invasive cardiac output evaluation during a maximal progressive exercise test, using a new impedance cardiograph device. *European journal of applied physiology*, *85*(3-4), 202-207.

12. Schultz, M. G., Climie, R. E., Nikolic, S. B., Ahuja, K. D., & Sharman, J. E. (2012). Reproducibility of cardiac output derived by impedance cardiography during postural changes and exercise. *Artery Research*, *6*(2), 78-84.

13. Sengupta, P. P., Tajik, A. J., Chandrasekaran, K., & Khandheria, B. K. (2008). Twist mechanics of the left ventricle. *JACC: Cardiovascular Imaging*, *1*(3), 366-376.

14. Shaw, J. G., Johnson, E. C., Voyles, W. F., & GRenne, E. R. (1985). Noninvasive Doppler determination of cardiac output during submaximal and peak exercise. *Journal of Applied Physiology,* 59(3), 722-731.

15. Sime, W. E., Whipple, I. T., Berkson, D. M., Macintyre, W. C., & Stamler, J. (1972). Reproducibility of heart rate at rest and in response to submaximal treadmill and bicycle ergometer test in middle-aged men. *Medicine and science in sports*, *4*(1), 14-17.

16. Tordi, N., Mourot, L., Matusheski, B., & Hughson, R. L. (2004). Measurements of cardiac output during constant exercises: comparison of two non-invasive techniques. *International journal of sports medicine*, *25*(02), 145-149.

17. Vanfraechem, J. H. (1979). Stroke volume and systolic time interval adjustments during bicycle exercise. *Journal of Applied Physiology*, *46*(3), 588-592.

18. Weissler, A. M., Peeler, R. G., & Roehll, W. H. (1961). Relationships between left ventricular ejection time, stroke volume, and heart rate in normal individuals and patients with cardiovascular disease. *American heart journal*, *62*(3), 367-378.

Table 1 Subject Characteristics (n=21)

	Mean (±SD)
Age (years)	21.4 ± 0.5
IPAQ (MET·min·week^{-1})	4825.7 ± 801.1
Height (cm)	178.9 ± 2.0
Weight (Kg)	73.2 ± 2.7
BMI (Kg/m^2)	24.5 ± 0.5
VO_2 max (mL·Kg^{-1}·min^{-1})	51.5 ± 1.5

Table 2 Treadmill Protocol

Time	TM Speed (mph)	TM Grade (%)
0:01-0:59	2.6	0
1:00-1:59	3.1	1.5
2:00-6:59*	**3.6**	**2.5**
7:00-7:59	4	3.5
8:00-12:59*	**4**	**5.5**
13:00-13:59	4.6	0
14:00-14:59	5	1
15:00-15:59	5.3	2.5
16:00-16:59	5.6	5
17:00-17:59	6.1	6.5
18:00-18:59	6	10.5
19:00-19:59	6	14
20:00-20:59	6	16.5
21:00-21:59	6.2	17.5
22:00-99:59	6.4	18.5

*Data collected in final two minutes of the given stage was used for analysis.

Table 3A. Mean Values of Primary Hemodynamic Variables for TM1 and TM2.

	TM1	TM2
Moderate Intensity Stage VO_2 ($mL \cdot Kg^{-1} \cdot min^{-1}$)	19.9 ± 1.9	19.4 ± 1.5
Vigorous Intensity Stage VO_2 ($mL \cdot Kg^{-1} \cdot min^{-1}$)	28.7 ± 3.4†	28.3 ± 2.6†
Moderate Intensity Stage SV ($mL \cdot beat^{-1}$)	125.4 ± 16.4	127.6 ± 19.4
Vigorous Intensity Stage SV ($mL \cdot beat^{-1}$)	133.5 ± 17.6†	135.5 ± 22.2†
Moderate Intensity Stage SVi ($mL \cdot beat^{-1} \cdot m^{2-1}$)	63.7 ± 7.2	64.7 ± 7.5
Vigorous Intensity Stage SVi ($mL \cdot beat^{-1} \cdot m^{2-1}$)	68.7 ± 8.7†	68.5 ± 8.1†
Moderate Intensity Stage HR ($beats \cdot min^{-1}$)	116 ± 13	112 ± 10
Vigorous Intensity Stage HR ($beats \cdot min^{-1}$)	147 ± 15†	143 ± 13†
Moderate Intensity Stage CO ($L \cdot min^{-1}$)	14.4 ± 1.9	14.2 ± 2.2
Vigorous Intensity Stage CO ($L \cdot min^{-1}$)	19.7 ± 2.3†	19.4 ± 3.7†
Moderate Intensity Stage CI ($L \cdot min^{-1} \cdot m^{2-1}$)	7.3 ± 0.7	7.2 ± 0.9
Vigorous Intensity Stage CI ($L \cdot min^{-1} \cdot m^{2-1}$)	10.0 ± 1.0†	9.8 ± 1.4†

Mean (±SD). * indicates significance of <0.05 between TM1 and TM2 trials. † indicates significance of <0.05 within trial due to intensity.

Table 3B. Mean Values of Secondary Hemodynamic Variables for TM1 and TM2.

	TM1	TM2
Moderate Intensity Stage EDV (mL)	152.8 ± 25.9	157.6 ± 25.7
Vigorous Intensity Stage EDV (mL)	161.2 ± 24.9†	162.3 ± 29.1
Moderate Intensity Stage EF% (%)	83.1 ± 5.6	81.5 ± 6.1
Vigorous Intensity Stage EF% (%)	83.4 ± 8.3	84.1 ± 6.0
Moderate Intensity Stage SVR ($dyn \cdot s \cdot cm^{-5}$)	516.6 ± 71.1	515.6 ± 87.5
Vigorous Intensity Stage SVR ($dyn \cdot s \cdot cm^{-5}$)	399.9 ± 59.6†	393.7 ± 79.6†
Moderate Intensity Stage SVRi ($dyn \cdot s \cdot cm^{-5} \cdot m^{2-1}$)	1015.0 ± 134.8	1009.2 ± 143.2
Vigorous Intensity Stage SVRi ($dyn \cdot s \cdot cm^{-5} \cdot m^{2-1}$)	786.0 ± 116.9†	770.4 ± 140.0†
Moderate Intensity Stage CTi	348.4 ± 66.2	353.0 ± 81.0
Vigorous Intensity Stage CTi	389.8 ± 99.4	410.9 ± 88.6†
Moderate Intensity Stage VET (ms)	254.8 ± 19.8	249.5 ± 23.4
Vigorous Intensity Stage VET (ms)	216.6 ± 28.2†	222.2 ± 20.8†
Moderate Intensity Stage EDFR (%)	61.0 ± 10.7	66.7 ± 14.3
Vigorous Intensity Stage EDFR (%)	67.4 ± 19.8	64.1 ± 16.0
Moderate Intensity Stage LCWi ($Kg \cdot m \cdot m^{2-1}$)	9.3 ± 1.4	8.9 ± 1.5
Vigorous Intensity Stage LCWi ($Kg \cdot m \cdot m^{2-1}$)	13.2 ± 1.8†	12.5 ± 2.6†

Mean (±SD). * indicates significance of <0.05 between TM1 and TM2 trials. † indicates significance of <0.05 within trial due to intensity.

Table 4A. Primary Intraclass correlations, Standard Errors of the Estimate, and Coefficient of Variation for Hemodynamic Variables between TM1 and TM2.

Variable	ICC	p-value	SEE	CV
Moderate Intensity Stage VO_2 ($mL \cdot Kg^{-1} \cdot min^{-1}$)	0.897	<.001	1.002	2.7%
Vigorous Intensity Stage VO_2 ($mL \cdot Kg^{-1} \cdot min^{-1}$)	0.866	<.001	2.179	3.7%
Moderate Intensity Stage SV ($mL \cdot beat^{-1}$)	0.857	<.001	11.030	5.0%
Vigorous Intensity Stage SV ($mL \cdot beat^{-1}$)	0.761	0.001	14.216	7.8%
Moderate Intensity Stage SVi ($mL \cdot beat^{-1} \cdot m^{2-1}$)	0.796	<.001	5.593	5.0%
Vigorous Intensity Stage SVi ($mL \cdot beat^{-1} \cdot m^{2-1}$)	0.745	0.002	7.266	6.9%
Moderate Intensity Stage HR ($beats \cdot min^{-1}$)	0.898	<.001	6.522	3.4%
Vigorous Intensity Stage HR ($beats \cdot min^{-1}$)	0.922	<.001	7.287	3.1%
Moderate Intensity Stage CO ($L \cdot min^{-1}$)	0.899	<.001	1.117	5.0%
Vigorous Intensity Stage CO ($L \cdot min^{-1}$)	0.862	<.001	1.365	7.2%
Moderate Intensity Stage CI ($L \cdot min^{-1} \cdot m^{2-1}$)	0.837	<.001	0.535	5.0%
Vigorous Intensity Stage CI ($L \cdot min^{-1} \cdot m^{2-1}$)	0.752	0.002	0.847	7.2%

Table 4B. Secondary Intraclass correlations, Standard Errors of the Estimate, and Coefficient of Variation for Hemodynamic Variables between TM1 and TM2.

Variable	ICC	p-value	SEE	CV
Moderate Intensity Stage EDV (mL)	0.811	<.001	19.421	7.4%
Vigorous Intensity Stage EDV (mL)	0.848	<.001	17.279	7.1%
Moderate Intensity Stage EF% (%)	0.722	0.003	4.699	3.8%
Vigorous Intensity Stage EF% (%)	0.852	<.001	5.413	3.1%
Moderate Intensity Stage SVR ($dyn \cdot s \cdot cm^{-5}$)	0.841	<.001	49.742	6.0%
Vigorous Intensity Stage SVR ($dyn \cdot s \cdot cm^{-5}$)	0.887	<.001	34.564	6.7%
Moderate Intensity Stage SVRi ($dyn \cdot s \cdot cm^{-5} \cdot m^{2-1}$)	0.791	0.001	105.757	6.0%
Vigorous Intensity Stage SVRi ($dyn \cdot s \cdot cm^{-5} \cdot m^{2-1}$)	0.864	<.001	76.652	6.7%
Moderate Intensity Stage CTi	0.820	<.001	48.565	8.7%
Vigorous Intensity Stage CTi	0.864	<.001	64.338	10.5%
Moderate Intensity Stage VET (ms)	-0.44	0.537	20.404	7.3%
Vigorous Intensity Stage VET (ms)	0.614	0.02	25.713	6.9%
Moderate Intensity Stage EDFR (%)	0.620	0.011	9.553	12.4%
Vigorous Intensity Stage EDFR (%)	0.853	<.001	13.157	9.5%
Moderate Intensity Stage LCWi ($Kg \cdot m \cdot m^{2-1}$)	0.772	0.001	1.181	8.2%
Vigorous Intensity Stage LCWi ($Kg \cdot m \cdot m^{2-1}$)	0.725	0.002	1.516	10.0%

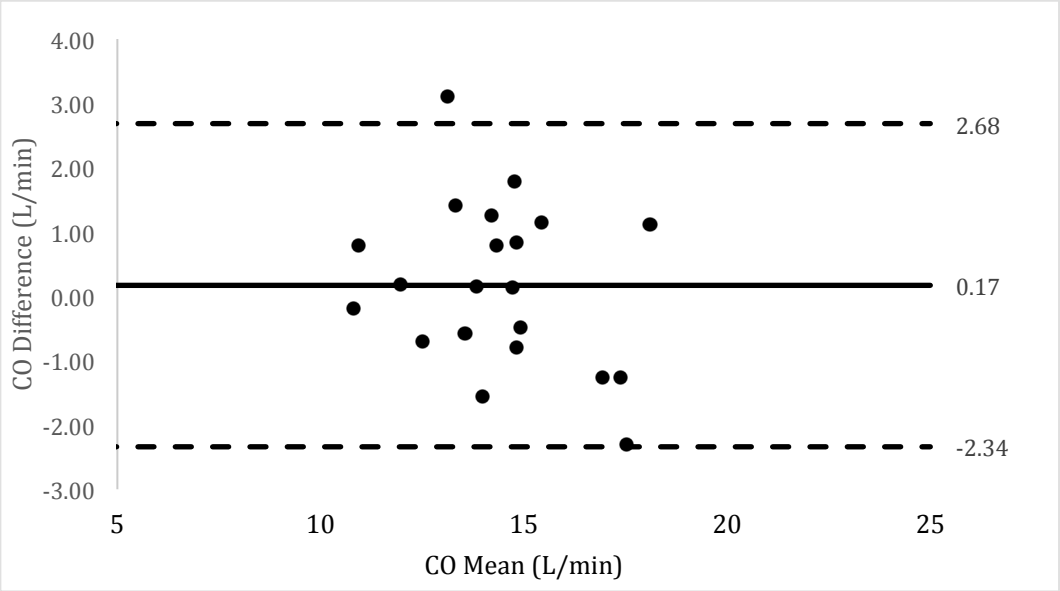

Figure 1A. Bland-Altman plot of Moderate Intensity Stage CO. Solid line indicates mean difference and dashed line indicates 2SD.

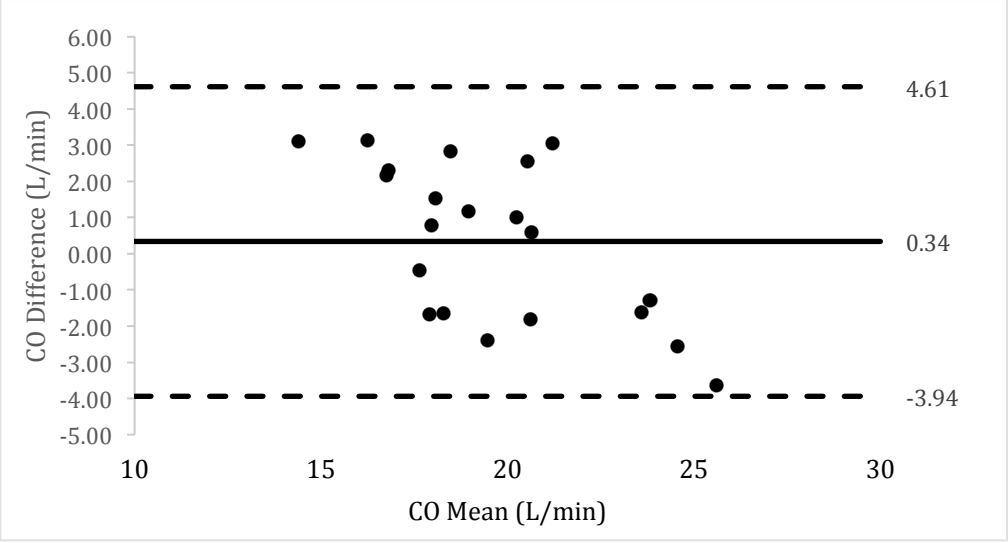

Figure 1B. Bland-Altman plot of Vigorous Intensity Stage CO. Solid line indicates mean difference and dashed line indicates 2SD.

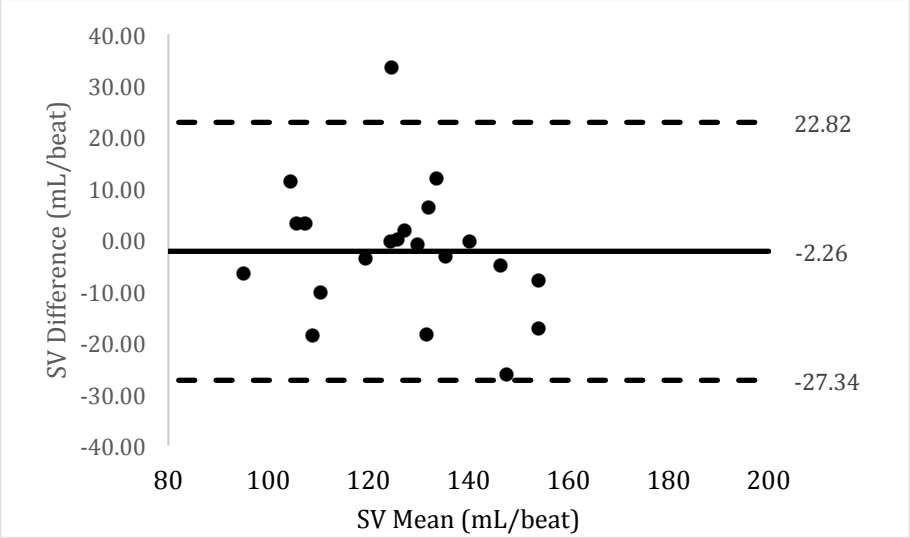

Figure 2A. Bland-Altman plot of Moderate Intensity Stage SV. Solid line indicates mean difference and dashed line indicates 2SD.

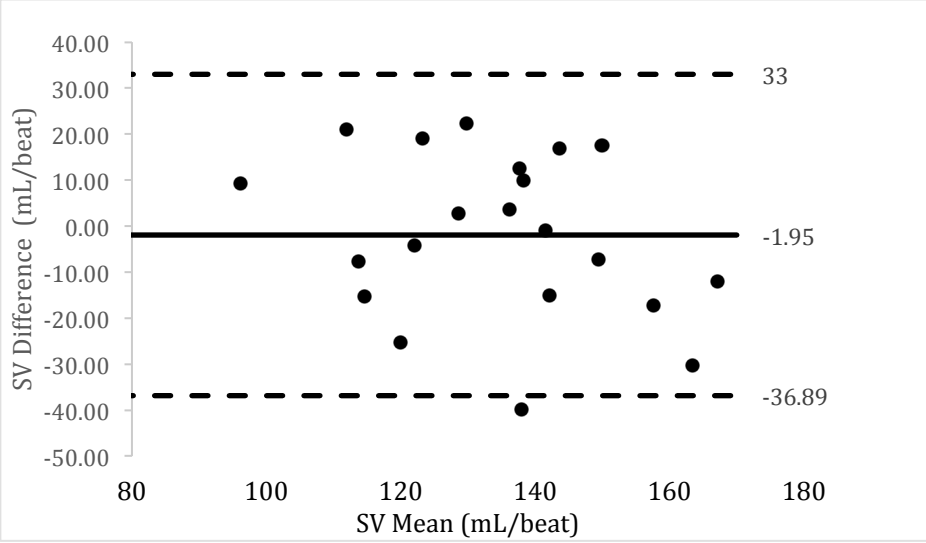

Figure 2B. Bland-Altman plot of Vigorous Intensity Stage SV. Solid line indicates mean difference and dashed line indicates 2SD.

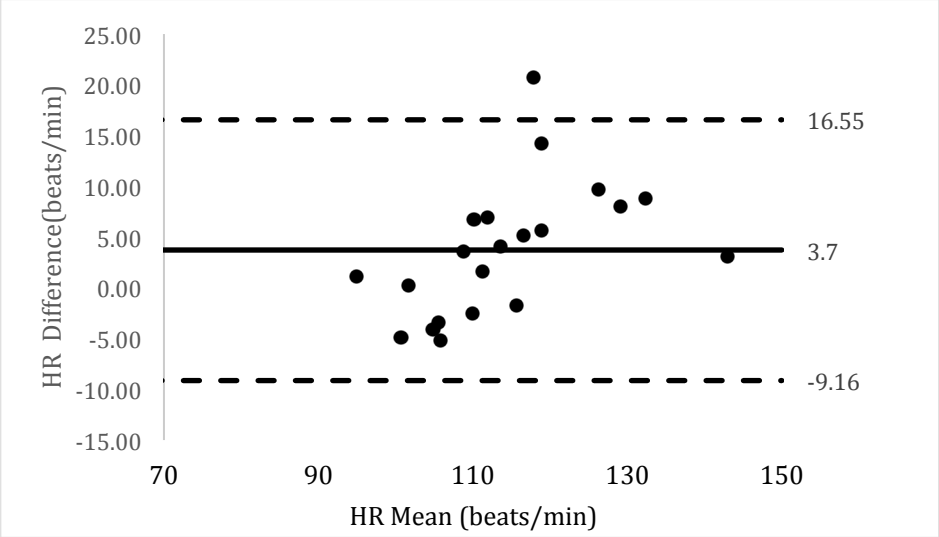

Figure 3A. Bland-Altman plot of Moderate Intensity Stage HR. Solid line indicates mean difference and dashed line indicates 2SD.

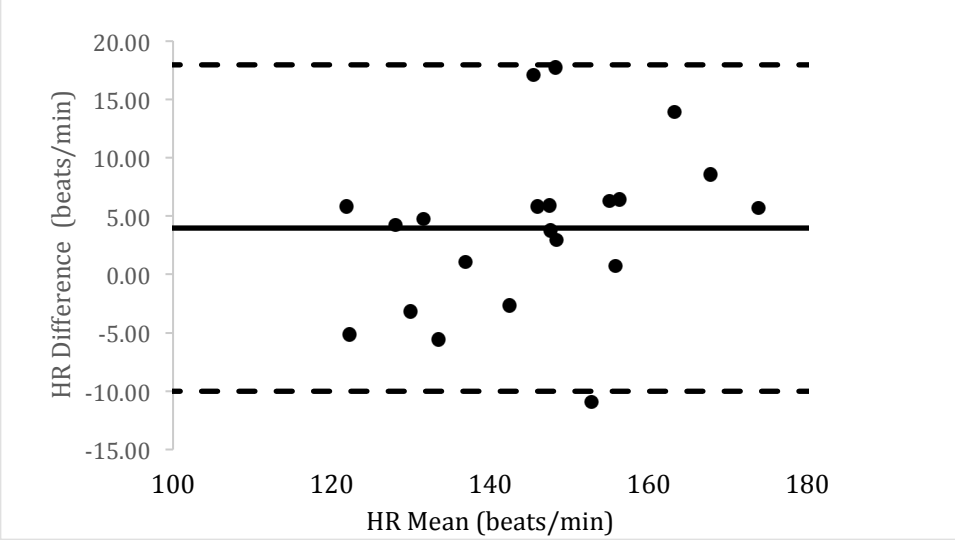

Figure 3B. Bland-Altman plot of Vigorous Intensity Stage HR. Solid line indicates mean difference and dashed line indicates 2SD.

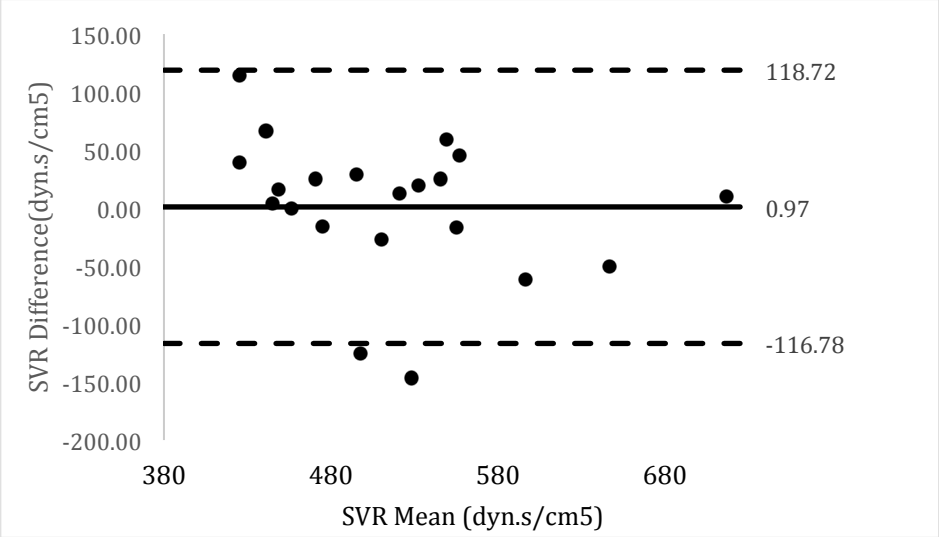

Figure 4A. Bland-Altman plot of Moderate Intensity Stage SVR. Solid line indicates mean difference and dashed line indicates 2SD.

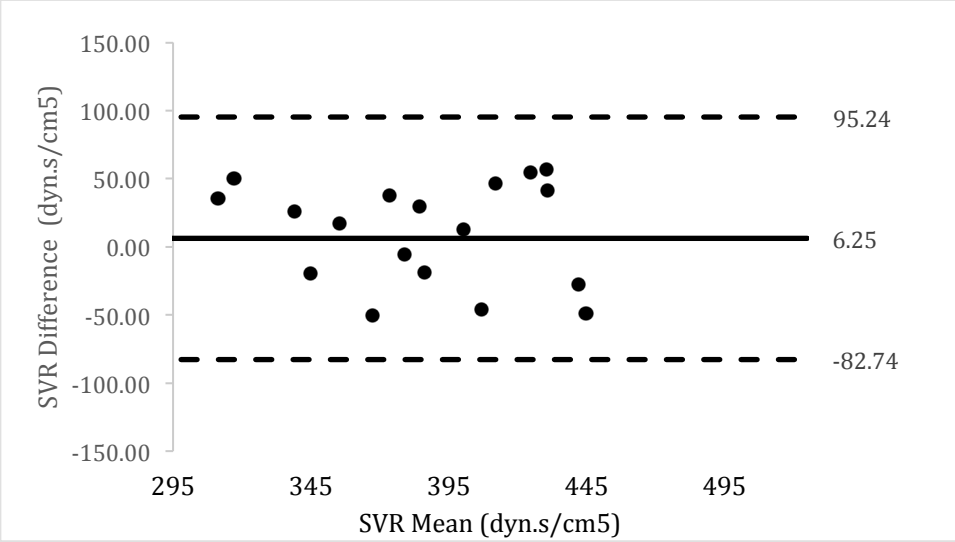

Figure 4B. Bland-Altman plot of Vigorous Intensity Stage SVR. Solid line indicates mean difference and dashed line indicates 2SD.

Appendix A

Email Recruitment Statement

Cardiovascular Research at James Madison University

Researchers at James Madison University's Department of Kinesiology are conducting a study to assess the reliability of a non-invasive cardiovascular assessment device during exercise. We are looking for:

- Individuals 18 years and older
- Not currently smoking
- Are without significant heart, lung or metabolic disease
- Have no serious orthopedic or bone problems that prevent vigorous exercise
- Are on no medications

The study would require subjects to undergo 4 maximal exercise tests, 2 on a treadmill and 2 on a bike, over the course of 4 visits to the James Madison University Human Performance Laboratory. Subjects will receive report on their aerobic fitness. If you are interested in volunteering, please email the research staff.

Appendix B

Informed Consent

James Madison University
Department of Kinesiology
Informed Consent

Purpose

You are being asked to volunteer for a research study conducted by Dr. Trent Hargens from James Madison University entitled, "Reliability of Impedance Cardiography in the Measurement of Cardiovascular Hemodynamics During Exercise".

The goal of this study is to examine whether a method for non-invasively measuring cardiovascular measures is repeatable on multiple days and on multiple exercise modes.

Experimental Procedures

You will be asked to visit the Human Performance Laboratory (HPL) in Godwin Hall 4 times over the course of about 2 – 4 weeks. Your total time commitment for participation in this study will be about 4 hours (each visit about an hour).

Upon completion of this informed consent, you will be asked to complete 2 short questionnaires, 1 that asks about your ability to participate in physical activity, and 1 that asks about your current level of physical activity participation. Each of these questionnaires should take about 5 minutes to complete.

You will then have your height and weight measured. Upon completion of this, you will be asked to complete a maximal treadmill exercise test. During the test, researchers will monitor your heart rate, blood pressure and your perceived exertion to the workload you will be doing. You will have several electrode patches placed on your skin on your torso, back and neck. These will be connected to the device measuring the variables we are interested in studying. During the test, you will breathe only through a mouthpiece, with your nose clamped off, so that we can measure the amount of oxygen you use during exercise. The treadmill will start with a very slow speed and little grade, and will steadily increase in speed and grade throughout the test, so it will start easy, and become very intense. At the end of the test, it should be a best effort on your part. It may be as hard as any exercise you remember doing. The exercise test will last about 10 – 15 minutes. Prior to your arrival to the HPL that day, you will be asked to refrain from eating for 4 hours prior to your arrival, and to avoid caffeine and alcohol for that time period as well.

Upon completion of this visit, you will be asked to return to the HPL 3 subsequent times, a minimum of 48 hours later, and at the same time of day as the first visit. The remaining 3 visits will consist of an additional maximal treadmill test, identical to your visit 1, or a maximal cycle exercise test. For the cycle test, you will be asked to pedal a cycle ergometer at a certain work rate that will steadily increase in difficulty until you are no longer able to maintain at least 50 rpm. It will start fairly easy, and become very intense, in a similar fashion to the treadmill. We will measure the same things during the cycle test as we do during the treadmill test. What type of test you complete (treadmill or cycle) for visits 2 – 4 will be randomized.

Risks

There is a risk of abnormal changes during the maximal exercise tests. These changes may include abnormal blood pressure, fainting, heart rhythm disorders, stroke, heart attack, and death. The chance of serious heart problems during maximal exercise among adults is very small (less than 1/10,000 maximal exercise tests). Every effort will be made to minimize risks of an abnormal response by reviewing you health history and providing adequate supervision of the exercise test. All staff are certified by the American Heart Association in BLS (Basic Life Support), and all tests will be supervised by individuals certified by the American College of Sports Medicine.

Benefits

Participation may include knowledge about your health status. You will receive information on your cardiovascular fitness.

Inquiries

If you have any questions or concerns or you would like to receive a copy of the final aggregate results of this study, please contact Dr. Trent Hargens at hargenta@jmu.edu or (540) 568-5844.

Questions about Your Rights as a Research Subject
Dr. David Cockley
Chair, Institutional Review Board
James Madison University
(540) 568-2834
cocklede@jmu.edu

Confidentiality

All data and results will be kept confidential. You will be assigned an identification number and a pseudonym in place of your real name. At no time will your name be identified with your individual data. The researcher retains the right to use and publish non-identifiable data. All paper data will be kept secured in a locked cabinet in a locked office. All electronic data will be kept on a password-protected computer in encrypted file folders. Upon completion of the study, only de-identified data will be kept for research dissemination purposes, and will be kept indefinitely. All material containing identifiable information will be destroyed. Final aggregate results will be made available to participants upon request.

Freedom of Consent

Your participation is entirely voluntary. You are free to choose not to participate. Should you choose to participate, you can withdraw at any time without consequences of any kind.

I have read this consent form and I understand what is being requested of me as a participant in this study. I freely consent to participate. I have been given satisfactory answers to my questions. The investigator provided me with a copy of this form I requested it. I certify that I am at least 18 years of age. By clicking "Yes" to the question below and submitting this confidential online survey, I am consenting to participate in this research.

Appendix C

PAR-Q

PAR-Q & YOU

(A questionnaire for People Aged 15-69)

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

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

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

YES ☐ NO☐	**1. Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?**
YES ☐ NO☐	**2. Do you feel pain in your chest when you do physical activity?**
YES ☐ NO☐	**3. In the past month, have you had chest pain when you were not doing physical activity?**
YES ☐ NO☐	**4. Do you lose your balance because of dizziness or do you ever lose consciousness?**
YES ☐ NO☐	**5. Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?**
YES ☐ NO☐	**6. Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?**
YES ☐ NO☐	**7. Do you have a diabetes or thyroid condition?**
YES ☐ NO☐	**8. Do you know of any other reason why you should not do physical activity?**

If you answered "Yes":

YES to one or more questions

A medical clearance form is required of all participants who answer 'yes' to any of the eight PAR-Q questions.
Note: Personal training staff reserve the right to require medical clearance from any client they feel may be at risk.

- Discuss with your personal doctor any conditions that may affect your exercise program.
- All precautions must be documented on the medical clearance form by your personal doctor.

NO to all questions

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

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

DELAY BECOMING MUCH MORE ACTIVE:

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

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

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

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

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

NAME_____

SIGNATURE_____**DATE**_____
_

SIGNATURE OF PARENT or GUARDIAN_____

WITNESS_____

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

Supported by: Health Canada Santé Canada

Physical Activity Readiness Questionnaire – PAR-Q

(revised 2006 by CW)

Appendix D

IPAQ

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

   _____ **days per week**

   ☐ No vigorous physical activities → ***Skip to question 3***

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

   _____ **hours per day**

   _____ **minutes per day**

   ☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

   _____ **days per week**

   ☐ No moderate physical activities → ***Skip to question 5***

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

   _____ **hours per day**

   _____ **minutes per day**

☐ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____ **days per week**

☐ No walking → ***Skip to question 7***

6. How much time did you usually spend **walking** on one of those days?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

_____ **hours per day**

_____ **minutes per day**

☐ Don't know/Not sure

This is the end of the questionnaire, thank you for participating

Bibliography

1. Borlaug B. A. & Kass D. A. (2009). Invasive hemodynamic assessment in heart failure. *Heart failure clinics,* 5(2), 217-228.
2. Charloux, A., Lonsdorfer-Wolf, E., Richard, R., Lampert, E., Oswald-Mammosser, M., Mettauer, B., & Lonsdorfer, J. (2000). A new impedance cardiograph device for the non-invasive evaluation of cardiac output at rest and during exercise: comparison with the "direct" Fick method. *European journal of applied physiology,* 82(4), 313-320.
3. Courtois, M., Mechem, C. J., Barzilai, B., & Ludbrook, P. A. (1992). Factors related to end-systolic volume are important determinants of peak early diastolic transmitral flow velocity. *Circulation*, *85*(3), 1132-1138.
4. Ekelund, U., Sepp, H., Brage, S., Becker, w., Jakes, R., Hennings, M., & Wareham, N. J. (2006). Criterion-related validity of the last 7-day, short form of the International Physical Activity Questionnaire in Swedish adults. *Public health nutrition,* 9(02), 258-265.
5. Fegler, G. (1957). The reliability of the thermodilution method for determination of cardiac output and blood flow in central veins. *Quarterly journal of experimental physiology and cognate medical sciences,* 42(3), 254-266.
6. Haites N. E, McLennan F. M., Mowat D. H., & Rawles J. M. (1985). Assessment of cardiac output by the Doppler ultrasound technique alone. *British heart journal,* 53(2), 123-129.

7. Haryadi, D. G., Orr, J. A., Kuck, K., McJames, S., & Westenskow, D. R (2000). Partial CO2 rebreathing indirect Fick technique for non-invasive measurement of cardiac output. *Journal of clinical monitoring and computing,* 16(5-6), 361-374.

8. Hoeper, M. M., Maier, R., Tonger, J., Niedermeyer, J., Hohlfeld, J. M., Hamm, M. & FAbel, H. (1999). Determination of cardiac output by the Fick method, theremodilution, and acetylene rebreathing in pulmonary hypertension. *American Journal of Respirtatory and Critical Care Medicine,* 160(2). 535-541.

9. Huntsman, L. L., Stewart, D. K., Barnes, S. R., Franklin, S. B. Colocousis J. S., & Hessel, E. A. (1983). Noninvasive Doppler determination of cardiac output in man. Clinical Validation. *Circulation,* 67(3), 593-602.

10. Jennings, G., Nelson, L., Nestel, P., Esler M., Korner, P, Burton D., & Bazelmans J. (1986). The effects of changes in physical activity on major cardiovascular risk factors, hemodynamics, sympathetic function, and glucose utilization in man: a controlled study of four levels of activity. *Circulation,* 73(1), 30-40.

11. Jones J. (2011). A new frontier for cardiac monitoring. NASA Spinoff, Retrieved from http://www.nwtcc.com/assets/BioZ.pdf

12. Kubicek, W. G., Patterson, R. P., & Witsoe, D. A. (1970). Impedance cardiography as a noninvasive method of monitoring cardiac function and other parameters of the cardiovascular system. *Annals of the New York Academy of Sciences,* 170(2), 724-732.

13. Laszlo G. (2004). Respiratory measurements of cardiac output: from elegant idea to useful test. *Journal of Applied Physiology.* 96(2), 428-437.

14. Lund-Johansen, P. (1990). The dye dilution method for measurement of cardiac output. *European heart journal,* 11(suppl 1), 6-12.

15. Moon, M. R., Ingels, N. B., Daughters, G. T., Stinson, E. B., Hansen, D. E., & Miller, D. C. (1994). Alterations in left ventricular twist mechanics with inotropic stimulation and volume loading in human subjects. *Circulation*, *89*(1), 142-150.

16. Ng, H. W., Walley, T., Tsao, Y., & Breckenridge, A. M. (1991). Comparison and reproducibility of transthoracic bioimpedance and dual beam Doppler ultrasound measurement of cardiac function in healthy volunteers. *British journal of clinical pharmacology*, *32*(3), 275-282.

17. Pescatello L. S., and American College of Sports Medicine. (2014). *ACSM's Guidelines for Exercise Testing and Presciption (9th edition.)*. Baltimore, MD: Wolters Kluwer/Lippincott Williams & Wilkins Health.

18. Pickett B. R. & Buell J. C. (1992). Validity of cardiac output measurement by computer-averaged impedance cardiography, and comparsion with simultaneous thermodilution determinations.

19. Powers, S. & Howley, E. (2014). *Exercise Physiology: Theory and Application to Fitness and Performance* (Ninth Ed.). McGraw-Hill Education.

20. Pugsley, J., & Lerner, A. B. (2010). Cardiac output monitoring: is there a gold standard and how to the newer technologies compare?. *Seminars in cardiothoracic and vascular anesthesia,* (p. 1089253210386386) SAGE Publications.

21. Richard, R., Lonsdorfer-Wolf, E., Charloux, A., Doutreleau, S., Buchheit, M., Oswald-Mammosser, M., ... & Lonsdorfer, J. (2001). Non-invasive cardiac output evaluation during a maximal progressive exercise test, using a new impedance cardiograph device. *European journal of applied physiology*, *85*(3-4), 202-207.

22. Schultz, M. G., Climie, R. E., Nikolic, S. B., Ahuja, K. D., & Sharman, J. E. (2012). Reproducibility of cardiac output derived by impedance cardiography during postural changes and exercise. *Artery Research*, *6*(2), 78-84.

23. Sengupta, P. P., Tajik, A. J., Chandrasekaran, K., & Khandheria, B. K. (2008). Twist mechanics of the left ventricle. *JACC: Cardiovascular Imaging*, *1*(3), 366-376.

24. Shaw, J. G., Johnson, E. C., Voyles, W. F., & GRenne, E. R. (1985). Noninvasive Doppler determination of cardiac output during submaximal and peak exercise. *Journal of Applied Physiology,* 59(3), 722-731.

25. Sime, W. E., Whipple, I. T., Berkson, D. M., Macintyre, W. C., & Stamler, J. (1972). Reproducibility of heart rate at rest and in response to submaximal treadmill and bicycle ergometer test in middle-aged men. *Medicine and science in sports*, *4*(1), 14-17.

26. Swan, H. J. C., & Ganz, W. (1983). Hemodynamic measurements in clinical practice: a decade in review. *Journal of the American College of Cardiology,* 1(1), 103-113.

27. Tordi, N., Mourot, L., Matusheski, B., & Hughson, R. L. (2004). Measurements of cardiac output during constant exercises: comparison of two non-invasive techniques. *International journal of sports medicine*, *25*(02), 145-149.

28. Vanfraechem, J. H. (1979). Stroke volume and systolic time interval adjustments during bicycle exercise. *Journal of Applied Physiology*, *46*(3), 588-592.

29. Weissler, A. M., Peeler, R. G., & Roehll, W. H. (1961). Relationships between left ventricular ejection time, stroke volume, and heart rate in normal individuals and patients with cardiovascular disease. *American heart journal*, *62*(3), 367-378.