Validation of VO₂max Assessment and Magnetic Resonance Cardiac Function
Measurements Utilizing an MRI Compatible Treadmill

THESIS

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Abstract

Maximum oxygen consumption (VO_2max) is considered the gold standard for assessment of cardiorespiratory fitness. Likewise, MRI is considered the gold standard for quantification of cardiac function; however, the MRI-compatible equipment required to combine these two measures has not been available to date. We utilized a specially designed MRI-compatible treadmill, and modified oxygen uptake equipment to eliminate the ferromagnetic components of the mask and headgear to perform a standard VO_2max treadmill test immediately adjacent to a clinical MRI system. We sought to determine if values for a VO_2max test performed in an MRI room utilizing MRI-compatible equipment were valid and accurate when compared to those obtained in an exercise lab with typical equipment set up. Ten recreationally trained subjects completed two VO_2max tests to volitional fatigue in two different settings; an exercise lab and an MRI room. Oxygen and carbon dioxide were measured continuously using a computerized system. Secondary criteria were assessed to confirm maximal exercise. Resting and peak exercise images of the heart were taken before and after maximal exercise to measure global cardiac function parameters including end systolic volume (ESV), end diastolic volume (EDV), cardiac output (CO) and left ventricular ejection fraction (LVEF). VO_2max values were different ($P=0.033$) between testing locations (47.6 ± 8.11 vs 50.0 ± 10.7). All subjects met or exceeded a $\text{RER} \geq 1.10$ and $\text{RPE} \geq 17$ at peak exercise.

(35.6 s. $\pm$ 3.8 s.) elapsed between the end of exercise and start of imaging. At rest vs immediately following peak stress, CO was (5.1 ± 1.0 vs 16.4 ± 5.6) and LVEF was (65.2 ± 3.3 vs 78.4 ± 4.8). Simultaneous VO_2max testing was completed in 7 recreationally trained healthy individuals for comparison of the inter-unit variability in two ParvoMedics TrueOne 2400 systems. Despite the equipment modifications required to measure VO_2max in the MRI environment, VO_2 measurements correspond to those obtained in the exercise lab. The differences in both separate and simultaneous testing produced <4-6% error, within acceptable criteria according to national certification bodies, manufacturers specifications, and previously published studies. MRI- VO_2max combined testing offers potential for advanced investigation of exercise physiology and cardiopulmonary disease.

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Table of Contents

Abstract	ii
Acknowledgments.....	iv
Vita.....	v
List of Tables	viii
List of Figures	ix
Chapter 1: Introduction	1
Chapter 2: Literature Review	4
Beginnings: Human Response to Exercise.....	4
Twentieth Century Contributions to Exercise Testing	5
International Influence of Exercise Science	7
VO ₂ max Testing: Validity and Protocol Design	9
Oxygen Consumption Measurement Instrumentation	12
Exercise Testing Modality	15
Clinical Stress Testing & Diagnosis.....	16
MRI and Cardiac Magnetic Resonance (CMR)	19
Chapter 3: Validation of VO ₂ max Assessment and Magnetic Resonance Cardiac Function Measurements Utilizing an MRI Compatible Treadmill	22
Introduction	22
Methods.....	24
Results	31
Discussion	37
Chapter 4: Conclusion.....	44
References.....	47

List of Tables

Table 3.1: Participant Descriptors	25
Table 3.2: Metabolic Data at Maximal Exertion.....	33

List of Figures

Figure 3.1: Cardiac Function CMR Cine Images of Heart	30
Figure 3.2: Comparison of Mean VO_2	31
Figure 3.3: Agreement and Interchangability of Measures.	35
Figure 3.4: Cardiac Function Measures Rest and Stess	36

Chapter 1: Introduction

Physiological measurement of oxygen consumption (VO_2) was first recorded in the 18th century A.D. Oxygen consumption measurement has long been associated with exercise and metabolic demands placed on the body. Maximal oxygen consumption ($\text{VO}_{2\text{max}}$) is a measure of the body's ability to utilize oxygen for metabolic processes during exercise stress. $\text{VO}_{2\text{max}}$ is a fundamental measure of cardiovascular and aerobic fitness. $\text{VO}_{2\text{max}}$ testing methodology was first established and explained in 1922 by Archibald Vivian (AV) Hill and colleagues [1-4]. Much of contemporary understanding involving maximal oxygen consumption and exercise plateau stems from the contributions of AV Hill in the early 1900's.

Physiological research and testing of human response to exercise increased drastically following World War II. Much of the work that provides modern foundational basis for exercise testing was completed in the mid twentieth century. Institutions such as the Harvard Fatigue Laboratory established themselves through research breakthroughs in the United States during the mid-1950's [2]. The American College of Sports Medicine was formed in 1954, with the mission of advancing health, through science education and medicine [1]. It was around this same time that many modern exercise scientists began to publish descriptive work specifically addressing human response to exercise. It was not

until 1975 that there was significant clinical and disease related application of VO₂max exercise testing [5]. VO₂max has been repeatedly cited as an excellent instrument for diagnosis and prediction of disease [6-8]. Consistent research data has contributed to the American College of Sports Medicine's recognition of VO₂max as the number one quantitative indicator of all-cause mortality in humans [6, 9].

Technological advancements have enhanced efficiency and streamlined testing methods which provide greater application in the clinical health setting. Maximal oxygen consumption contributes valuable information to clinicians and healthcare providers. Combination testing and imaging techniques involving exercise or pharmacological stress, enhance the sensitivity, specificity, and offer improved diagnostic ability to health care professionals compared to resting clinical VO₂ assessment [9-13]. In clinical patient populations, exercise stress testing is favored over pharmacological when applicable. Research suggests, there are reductions in cardiac function, such as ventricular muscle wall tension, peak systolic stress, and left ventricular volume measures associated with dobutamine and other pharmacological stress testing methods compared to exercise stress testing [14]. However, there are specific clinical populations in which pharmacological stress testing may be utilized preferentially; if patients are unable to safely complete exercise, or medications limit the effectiveness of exercise to produce physiological cardiac stress required [14, 15]. Exercise places stress on the body that enhances clinical precision in identifying signs or symptoms of disease. Proper and timely diagnosis is critical to planning and administering efficacious treatment in patient populations.

VO₂max is a fundamental, gold standard measure of cardiorespiratory fitness. Similarly, magnetic resonance imaging (MRI) offers many benefits to cardiac function measurement; including a high temporal, spatial, and contrast resolution in a single technique, MRI completely meets many requirements of a gold standard [16]. Exercise stress cardiac magnetic resonance (CMR) has recently become feasible due to development of imaging techniques along with a novel MRI-compatible treadmill [17]. To date there have been no published studies that assess the feasibility, validity, and reliability of VO₂max testing utilizing an MRI compatible treadmill in conjunction with CMR. The purpose of this present research is to (1) assess the viability and efficacy of VO₂max testing utilizing an MRI-compatible treadmill to induce exercise stress for CMR measures versus a standard VO₂max exercise stress testing set up with an electronically driven motor treadmill, and (2) determine the variability in VO₂max in two ParvoMedics TrueOne 2400 automated systems when utilized in a clinical MRI room setting compared to an exercise lab.

Chapter 2: Review of Literature

Beginnings: Human Response to Exercise

The beginnings of sport and exercise science can be traced back to Ancient Greece, with the advent of the Olympic Games. Human function was extensively studied by scientists in Ancient Greece and continues to be a major area of research study. Throughout history significant effort has been put forth in an attempt to understand the physical workings and benefits of exercise on the human body. Although medicine practiced in ancient Greece was rudimentary, the term “exercise”, specifically as an adjunct to good health was commonly used in Hippocrates’ time around 400 B.C.E [1]. In the 17th century, prior to oxygen being scientifically defined, Cornelis Drebbel constructed a submarine capable of remaining underwater for up to three hours [18]. This 1621 A.D. submarine may represent potential origins of understanding exercise, work capacity, and the gas, defined later as oxygen; since in order to remain submerged for that amount of time oxygen was likely created by burning potassium nitrate to keep the rowers from becoming hypoxic [18]. Long before oxygen was scientifically defined, there was evidence of understanding the importance of human respiration.

One of the first documented “true” laboratory exercise experiments conducted by Antoine Lavoisier related muscular work to utilization and generation of an invisible, but measureable, gas he called “vital air” in the mid 1700’s [2, 18, 19]. It was not until 1774

that oxygen would be defined by a productive British researcher, Joseph Priestley [20]. Lavoisier's research showed there was an increase in oxygen consumption during sustained exercise, in heated environments, and after consumption of food [2]. The basis for exercise testing and performance measurement date back to the Olympics held in ancient Greece. Yet, continued dedication to understanding basic human functions by researchers such as Lavoisier, during the 18th and 19th centuries, set much of the foundation for continued work and enhanced understanding of modern exercise physiology.

Twentieth Century Contributions to Exercise Testing

The term “physiology” was first introduced by Jean Francoise Fernel in the 16th century. Although, human response to exercise had been studied previously, most agree that there was not an identifiable field of exercise physiology in existence until the 19th century [1]. In 1922 Archibald Vivian Hill (AV Hill) shared the Nobel Prize for Medicine or Physiology for his work on skeletal muscle with German biochemist Otto Fritz Meyerhof [1]. In this very same year, he and a colleague, Harley Lupton presented a paper “The oxygen consumption during running” [1, 4]. In this paper, Hill & Lupton describe changes in rate of oxygen consumption utilizing a discontinuous running protocol on a track and the Douglas Bag (DB) method. The subsequent years were productive for Hill as he followed up his 1922 work on exercise with several papers describing the skeletal muscle lactic acid production, factors governing athletic speed, recovery from fatigue, and the plateau oxygen utilization [1, 3, 4].

Although Hill was not the first to measure oxygen consumption in human exercise performance, his 1922 paper described data that was the highest recorded in physiological literature. Hill's research describing oxygen consumption plateau, similarly, was not the first documentation of this physiological process. Oxygen plateau was first noted by Liljestrand and Senstrom in 1920 [1]. The 1920 paper interpreted the plateau as increased running economy, or decreased need for oxygen, while Hill argued that the subjects needed, but could not get the oxygen required [1, 3, 4, 21]. The early work of AV Hill and colleagues acted as a spring board for continued discovery and growth in the field of exercise physiology, particularly in athletic oxygen consumption.

Throughout the early to mid-1900's, there was a surge in the field of exercise physiology throughout the industrialized regions of the world. In the United States, the Harvard Fatigue Lab was established in 1927. Although this lab was only active until 1947, the Harvard Fatigue Lab was involved in research that had broad reaching effects, citing over 350 publications and performing research on wartime nutrition and environmental factors affecting performance of American soldiers [2, 18, 22]. Among the many accomplishments of the Harvard Fatigue Lab, the greatest contribution to the field was a generation of "exercise physiologists" who brought their research interests in exercise science with them building up research programs throughout the United States and abroad [18]. The Laboratory of Physiological Hygiene, University of Minnesota, Minneapolis, Minnesota was one of many successful American research labs that grew from the Harvard Fatigue Lab. This laboratory further developed maximal exercise oxygen consumption testing methods. Many experiments were completed that built upon,

and improved, current testing methodology such as mouthpiece diameter, limitations on ventilation, speed versus grade changes, importance of warm up, test-retest reliability, and criteria for identification of plateau in VO₂ [18, 23]. The first sixty years of the twentieth century was a time of tremendous growth in the field of exercise physiology; during this time early research laboratories constructed a foundation on which exercise testing and VO₂max measurement could be refined for future athletic and clinical application.

International influence on Exercise Science Development

Maximal exercise testing developed almost simultaneously throughout the industrialized world during the first half of the twentieth century. Many of the testing methodologies derived are still the foundation on which modern testing procedures have been developed. There were numerous contributions to exercise testing research during this time, yet some of the most influential labs were located in Denmark, Sweden, Norway, Finland, England, and the United States of America [1, 2].

Johannes Lindhard and August Krogh were two eminent Danish researchers. Their work, heavy in physiological chemistry, focused on gas exchange in the lungs and macronutrient combustion for fuel at rest and exercise. Their work with diet and exercise lead to the publication of a lengthy report, *The relative value of fat and carbohydrate as sources of muscular energy*, published in 1920 [2, 24]. This report provides an introduction and explanation with supporting evidence of Respiratory quotient (RQ) or respiratory exchange ratio (RER). Other major contributions are credited to three active scholars who published numerous papers between the 1930's and 1970's. Erik

Christensen, Marius Nielsen, and Erling Asmussen, who was initially an assistant in Lindhard's laboratory, coauthored articles delineating ventilatory and cardiovascular response to changes in posture and exercise intensity, maximum working capacity during arm and leg exercise, and changes in oxidative response of muscle during exercise [2]. Early and significant contributions may be traced back to Denmark, where a team of award winning Danish researchers was at the cutting edge of describing much of the biochemistry behind physiological exercise stress. Work with diet, RQ and exercise intensity lead to many break through findings including the suggestion of carbohydrate loading for endurance exercise activity in 1939 [2].

Swedish professor Per-Olaf Astrand, MD, PhD is a renowned researcher of exercise physiology. Astrand, a student of Erik Christensen, established a line of research stemming from his dissertation, which examined physical working capacity of both sexes ages 4 to 33 years, that quickly shifted him to the forefront of experimental exercise physiology, where he has achieved worldwide fame in the field exercise science [2]. Much of Astrand's research involved assessment of the effects intermittent cycling exercise have on VO_2 . Cycle ergometry exercise assessment techniques developed and first explained by Astrand are commonly used in modern exercise physiology testing.

Norwegian and Finnish influences ushered in a new generation of exercise physiologists, equipped with instruments that expedited exercise measurements especially, gas analysis. In the late 1940's respiratory gases could be analyzed by highly accurate sampling apparatus that measured small quantities of carbon dioxide and oxygen in expired air. Gas analysis methodology and the analysis instruments were developed by

Norwegian scientist Per Scholander and John Scott Haldane [2]. Prior to gas analysis instrumentation being devised, methods involved countless time consuming processes for a single experiment, which generally were frequently completed in duplicate for increased accuracy. For this reason, many early exercise physiology and metabolism studies were completed using sample sizes of one or two subjects. The micro-Scholander and the Haldane analyzer system allowed for increased accuracy (± 0.015 mL/100mL), efficiency and consistency in gas measurement. Nordic contributions can be recognized throughout the field of exercise physiology.

In the United States of America, in the first half of the twentieth century, there was a similar history of rapid growth and simultaneous discovery. At the same time that Hill was looking at runners from Cornell during his visiting lectureship, Henderson and Haggard measured oxygen uptake in Yale rowers, Christiansen studied Danish cyclists, and Robinson, Edwards, & Dill added the recording of heart rate to that of oxygen consumption in testing elite athletes at the Harvard Fatigue Laboratory [1]. Although it was not until the mid-1950's that VO₂max testing became standardized, there were many competing laboratories that almost simultaneously developed and tested various VO₂max testing procedures and methodologies.

VO₂max Testing: Validity and Protocol Design

In the year 1922 British physiologist, AV Hill, and colleagues first published research that showed evidence suggestive of VO₂max, a phenomenon that has been tested, debated, and confirmed for more than eight decades. Using a discontinuous

exercise protocol consisting of several of 3-4 minute periods at set track running speeds 6.4, 7.4, 9.1, and 10 miles per hour (mph), VO_2 increased as running speed increased until 9.1 mph was reached [1, 3]. It was shown there was a plateau in oxygen consumption despite increased exercise load from 9.1 mph (4.175 l/min) to 10 mph (4.055 l/min) [1, 4]. It was a year later that Hill followed up with a publication that stated “However much the speed be increased beyond this limit, no further increase in oxygen intake can occur: the heart, lungs, circulation, and the diffusion of oxygen to the active muscle-fibers have attained their maximum activity” [21]. This statement has been the basis of much research and debate over the years, resulting in a great deal of literature dedicated to further exploring the concept and the viability of VO_2max .

In order to confirm that participants reach a maximal effort, research emphasis was placed on, secondary criteria, including measurement of blood lactate levels (LA) pre and post, peak RER, peak heart rate (HR_{max}), and peak rating of perceived exertion (RPE). Secondary criteria provide technicians some more variables to assess in order to confirm maximal exercise is achieved during testing. However, more recent research has focused on debating incidence of VO_2max plateau and potential for an updated primary criterion or set of criteria [1, 3, 25-28]. Critics of the classical AV Hill model, suggest that achievement of VO_2max is dependent on too many variables and that the incidence of VO_2 plateau is far too low, due to subject variability and identification of presence of “plateau”[25, 26]. Despite the controversy, research evidence supports a strong scientific argument for the traditional presence of a, maximal oxygen consumption, plateau model in which there are decades worth of research data that seem to provide support.

Early exercise testing research was similar to that of AV Hill and colleagues' work, focusing on examining human response to exercise using a discontinuous testing methodology. Exercise was completed in individual short periods, and would become increasingly intense with each new bout of exercise. In 1955, Taylor et al. used a discontinuous protocol design based upon 3 minute exercise stages that were 7 mph, at the conclusion of each 3 minute stage, intensity would increase via an increase in grade by 2.5% [23]. Taylor examined the reliability of this protocol using duplicate testing on separate days. As published the data showed a high reliability, with less than 1% variability in VO_2max from day to day [23]. Taylor's work resulted in data that showed a conserved increase in VO_2 with 2.5% grade increase during duplicate tests as well as demonstrating that VO_2 plateau was achieved in 108 of 115, or approximately 94%, of subjects [23].

Discontinuous VO_2max testing was lengthy, and inefficient, requiring subjects to test on separate days or with rest time between exercise bouts. In 1958, scientists measured VO_2 in a discontinuous test protocol, but only allowed only 10 minutes rest between exercise sessions, which resulted in tests that could be completed in a single day [29]. In this study, Mitchell et al utilized more specific quantifiable guidelines in order to identify plateau in VO_2 (VO_2 increase between stages, less than two standard deviations from the mean, 54 ml, increase between previous stage changes) [29]. Data from this research identifies 72% of individuals tested achieved a quantifiable plateau in VO_2 . Mitchell et al provided a stepping stone in which subsequent studies attempted to increase efficiency involved with exercise testing methods. Maksud and Coutts were

among some of the first researchers to publish data validating continuous, “graded exercise testing” in a study from 1971. Participants completed the protocol utilized in Taylor et al. 1955, but in a continuous fashion, where grade increases occurred every minute [30]. The Maksud and Coutts 1971 study allowed for similar studies to be conducted resulting in the conclusion that there were no differences between discontinuous versus continuous exercise testing on neither cycle nor treadmill modalities [30, 31]. Continuous graded exercise testing is the modern methodology commonly used today, due to increased efficiency without declines in measurement accuracy have significantly affected the usage of the discontinuous model. There is no doubt that improvements in gas analysis instrumentation have created an opportunity for efficiency and increased the frequency with which continuous graded, or ramp, exercise testing is performed.

Oxygen Consumption Measurement Instrumentation

Oxygen consumption measurement instruments have improved drastically since the micro-Scholander and Haldane devices were introduced. Each of those devices, although revolutionary for their time, would require significant time to calculate VO_2 from the data that was produced during a single exercise test session. The Douglas Bag method has long been considered the gold standard for measurement of oxygen consumption. This method involves capturing air samples throughout testing and measuring volume and concentration of gases subsequently. Modern instrumentation has become increasingly adapted for continuous automated data acquisition and provides real time displays of oxygen and carbon dioxide concentration. Continuous automated VO_2

measurement devices have allowed testing protocols to be adapted to fit the needs of the test modality and athlete.

Automated VO_2 measurement systems provide incredibly precise data. Sampling interval is one of many variables that can be adjusted when measuring VO_2max .

Although there is not a clear consensus on best practices for sampling interval adjustment, most agree that the sampling interval must be adapted to fit the test protocol and increase ability to identify VO_2max or plateau in oxygen consumption. Research states that incidence of VO_2 plateau can vary greatly from 12 to 100% [32]. Astorino has published data that supports usage of sampling intervals of 30 seconds or less for increased incidence of VO_2 plateau. Breath by breath (81%), 15 (91%), or 30 (89%) second data revealed the highest incidence of VO_2 plateau [32, 33]. It is important to select an accurate sampling interval for proper measurement of VO_2max especially in modern testing environments where ramp protocols are utilized more frequently than graded exercise.

Variability is an inevitable component of VO_2max testing. Temperature, humidity, composition and size of most recent meal, test modality, time of day, and equipment are common contributing sources for variability. Although some national certification bodies accept a variance of approximately 4% (2-3 ml/kg/min), individual VO_2max can vary significantly between test sessions by as much as 15% (5-10 ml/kg/min) [34, 35]. Variance in individual VO_2max can result from changes in motivation, knowledge, or tolerance of discomfort. Slight changes in VO_2max between testing sessions can be compounded by other effectors such as testing equipment

variability. Studies that have compared VO_2max testing instruments produced by different manufacturers have cited large discrepancies between the VO_2max achieved using various instruments to test the same population sample. Although reproducibility is cited consistently as less than five percent in the literature, between system differences are as high as 22% [34, 36]. These studies suggest that prescribing or evaluating exercise tests based upon VO_2max measured using different testing instruments may be unreliable.

ParvoMedics is a prominent manufacturer of oxygen consumption and cardiopulmonary health measurement equipment. Research has been conducted to assessing the variability and reliability of ParvoMedics, and similar, equipment. In a study by Crouter et al. 2006, the MedGraphics VO2000, and the ParvoMedics TrueOne 2400 were compared for reliability against the gold standard Douglas Bag method. This study tested the reliability of the three methods in between days cycle ergometer exercise testing. MedGraphics VO2000 (CV 14.2-15.8%) was less reliable than DB (CV 5.3-6.0%) and the TrueOne 2400 (4.7-5.7%) [37]. It was concluded based on this experiment that the ParvoMedics TrueOne 2400 is accurate and reliable for measurement of gas exchange variables [37]. Macfarlane et al. recently published a similar study in 2013 that tested the inter-unit variability of two ParvoMedics TrueOne 2400 systems. The results of this study were a within subject mean coefficient of variation (CV) of ~4% and a mean absolute percentage error (APE) of ~6%, while the inter-unit error was CV ~1.5% and APE ~2.1% [38]. A 1982 study by Katch et al. reported, using 80 repeated VO_2max trials with Douglas Bags, within-subject variation to be 5.6% [39]. The ParvoMedics TrueOne

2400 automated metabolic gas analysis platform has demonstrated reliability and variability that rival the gold standard DB method.

Exercise Testing Modality

Exercise modality has important implications on test results. Worldwide, the most common exercise test modality is the cycle ergometer. However, numerous studies have reported production of higher VO_2max (5-20% increase) with weight bearing versus weight supported exercise [2, 18, 31, 40-42]. Research conducted with 24 healthy male participants has shown treadmill exercise consistently results in increased VO_2max (mean 6.6% greater) compared to bicycle exercise [40]. This is likely due to an increased cardiac output and arterial versus venous blood oxygen content associated with weight bearing exercise activity, such as treadmill exercise, due to increased upper body and postural muscle mass being recruited. Similarly, another study shows, running on a treadmill at a 5.25% incline produced a 7% greater rate of maximal oxygen consumption than completing a discontinuous graded exercise test on a cycle ergometer [43]. This discrepancy in VO_2max is decreased in those who are well trained cyclists and when the treadmill test is completed with no added incline or grade increases [44]. Unless adapted and proficient in cycling, the treadmill modality provides a superior means of achieving VO_2max values during exercise testing. Treadmill testing may offer increased benefits for diagnostic and clinical applications of exercise testing due to increased cardiorespiratory demands.

Clinical Stress Testing & Diagnosis

Clinical exercise testing offers a cost efficient means of assessing health, wellness, and disease risk. Exercise stress testing has been conducted throughout the past 60 years to assess coronary artery disease risk [9, 10]. Governed by the American College of Cardiology (ACC) and the American Heart Association (AHA), there are several different types of clinical exercise tests that can be administered to patients. Although, treadmill stress testing is the preferred option for nearly all ambulatory patients, due to increased diagnostic sensitivity and specificity [10, 45-47]. Stress testing method and modality can be individualized based upon effectiveness and patient ability level in an effort to optimize diagnosis, prognosis, and patient safety.

Exercise and electrocardiogram (ECG) ie. symptom limited stress test is a common diagnostic tool used for both healthy and patient populations. This test can be completed using various modalities, but is usually completed with a treadmill or cycle ergometer. Cardiac ischemia, arrhythmias, and functional capacity may all be measured during exercise ECG stress testing [9, 10]. The exercise ECG stress test is usually employed as a preliminary test because of low relative cost and non-invasive nature. Exercise ECG testing has been extensively studied exhibiting a mean sensitivity and specificity of 68% and 77%, respectively [46]. This option has recognized limitations such as increased incidence of false positives for myocardial ischemia, particularly in women and in patients with underlying arrhythmias [10, 46]. Exercise ECG tests are often used to identify or confirm the existence of a potential health problem and provide clinicians with more information for creating a strategic diagnostic or treatment plan.

Despite valuable prognostic value, in many instances the exercise ECG stress test is most definitive in combination with other testing methods that assess either perfusion, or cardiac function.

Exercise stress echocardiography stress testing provides additional physiological function measures, ventricular function, flow velocity, myocardial wall thickness, wall motion, and valve motion, to clinicians. Testing may be completed utilizing exercise or pharmacological stress. Stress echo testing has benefits above and beyond exercise ECG and is indicated for those who are unable to exercise maximally or whom have uninterpretable ECG. Accuracy of stress echocardiography for detection of coronary artery disease (CAD) or stenosis ranges from 80-90%, exceeding exercise ECG [48]. In several significant studies with greater than 100 patients exercise stress echocardiography exhibits sensitivity and specificity ranging 74-97% and 64-86%, respectively [48]. Higher sensitivity may be obtained with cycle ergometer exercise, as ischemia is not lost during post exercise. However, a decline in specificity is also associated with this modality. Dobutamine stress echocardiography offers some enhancements in sensitivity and specificity, but can be compromised by medical treatment, side effects, or pharmacological agents [48]. Pharmacologically-aided stress testing decreases the workload on the heart reducing the validity of cardiac function measurements, such as velocity, stroke volume, or cardiac output during testing. Accuracy in stress echocardiography testing is heavily influenced by achievement of an ischemic threshold. It is important that pharmacological or exercise stress be adequate during testing to avoid

false negative diagnoses. Many of the limitations associated with stress echocardiography are due to poor image resolution and inability to assess multi-vessel disease.

Radionuclide cardiac perfusion, single photon emission computed tomography (SPECT), or nuclear multi gated acquisition (MUGA) stress testing may be recommended in order to evaluate hemodynamics and cardiac muscle blood flow, especially in those who have experienced potential signs and symptoms of cardiovascular or heart disease. Radionuclide angiography may be completed with exercise or pharmacological stress while stationary or during activity. Cardiac perfusion imaging, SPECT, is used to assess blockage in the coronary arteries, while radionuclide angiography, MUGA, scans are commonly used to evaluate blood flow and function, via ejection fraction measurement. Previous studies suggest overall sensitivity in detection of coronary disease was 91% with a specificity of 87% in patients, confirmed by angiography[49]. This testing is specialized for measuring blood flow within and to the heart muscle. Consequently, both SPECT and MUGA testing are invasive when compared to alternative testing procedures due to intravenous injection of tracer chemicals that can be identified during imaging throughout the cardiac cycle. Limitations of radionuclide perfusion study are exposure to ionizing radiation, elevated cost, and relatively invasive requirements of testing.

A large, rather impressive body of research describes current cardiovascular health benefits associated with aerobic exercise and clinical testing, states that they have tremendous prognostic value [5, 10, 42, 46, 50]. Yet, improvements in diagnostic capacity and accuracy are still possible. Proper modality, protocol and technique are

critical to effectiveness and accuracy during clinical stress testing. Common tests discussed previously, exercise ECG, stress echocardiography, SPECT and MUGA scans provide individual advantages and disadvantages. Recent research has been focused the use of MRI and computerized tomography (CT) scans as a potential well-rounded alternative to the testing methods frequently utilized.

MRI and Cardiac Magnetic Resonance (CMR)

Magnetic Resonance Imaging is a valuable tool relied on by modern healthcare professionals worldwide. MRI offers great advantages in image quality, but does not also subject patients to radiation or x-ray exposure. Cardiac magnetic resonance (CMR) is a robust assessment technique for heart function. CMR provides high resolution of wall motion, perfusion, blood flow, and myocardial viability [51]. The magnetic field required for MRI is arguably its most significant limitation. Conventional exercise equipment cycle ergometers and treadmills generally contain metallic components. Pharmacological stress testing is possible in an MRI environment; however exercise stress has been shown time and again to be preferential in clinical testing. Removal of ferromagnetic material from common hospital instruments and novel technological design in exercise equipment have provided both clinicians and researchers a unique opportunity for testing using the benefits of MRI.

Recently, an MR-safe treadmill was developed for trial use [51]. MR-compatible supine cycle ergometers have been available for some time [52, 53]. Supine cycle exercise allows for CMR imaging during activity, but this has not been shown to elicit the same physiological stress to the cardiovascular system as weight bearing treadmill

exercise [41, 43-45, 51]. Most individuals, unless well-trained cyclist, are unable to reach maximal cardiovascular exertion utilizing cycle modality prior to being limited by lower extremity fatigue. Treadmill exercise is superior to cycle ergometer exercise in producing increased cardiac demand and oxygen consumption, thus increasing stress test viability. Research suggests exercise CMR testing provides a feasible viable alternative to SPECT. A 2012 study completed in which CMR accuracy and prognosis was compared to that of SPECT resulted in 21/21 versus 17/21 detection of significant coronary artery disease (CAD) [17]. Prognosis confirmed 8-12 months following tests all patients with negative CMR or SPECT had had no coronary events [17]. Cardiac stress testing utilizing a treadmill and CMR provides enhanced opportunity for diagnosis, prognosis, evaluation, and research which leads to improved knowledge and treatment of patients by healthcare professionals.

Stress testing accuracy is optimized when patients reach maximal exertion or ischemic threshold in a positive test. Clinical stress testing is commonly administered based upon age predicted max heart rate (APMHR). True heart rate max is variable between individuals (± 12 bpm) decreasing its reliability as test endpoint criterion. Recent research claims, particularly in older populations, who are disproportionately represented in CAD, the standard APMHR equation ($220 - \text{Age}$) consistently underestimates true max heart rate [54]. Clinical stress testing based upon achieving an age predicted maximal heart rate (APMHR) or heart rate reserve (HRR) may be improved with the addition of oxygen consumption (VO_2) measurement. Confirmation of reaching maximum physiological exercise stress is achieved through identification plateau in VO_2 [1, 3, 4,

21]. Addition of VO₂ measurement to clinical exercise testing improves ability of technicians to ensure a valid test of patient capacity and assess heart function and markers of CAD.

Combination exercise CMR and VO₂max testing has yet to be evaluated for feasibility and validity. VO₂max testing represents the gold standard measure in cardiorespiratory fitness with many associated health implications. MRI offers many benefits to cardiac function measurement; offering a high temporal, spatial, and contrast resolution in a single technique, MRI completely meets many requirements of a gold standard [16]. Combination exercise CMR and VO₂max testing presents a potential advancement in application of clinical exercise testing to assess cardiopulmonary health. The purposes of the present study were (1) to assess the viability and efficacy of VO₂max testing utilizing an MRI-compatible treadmill to achieve maximal exercise stress prior to CMR measures versus a standard VO₂max exercise stress testing set up with an electronically driven motor treadmill, and (2) determine the variability in VO₂max in two ParvoMedics TrueOne 2400 automated systems when utilized in a clinical MRI room setting compared to an exercise lab during separate testing sessions.

Chapter 3: Validation of VO₂max Assessment and Magnetic Resonance Cardiac Function Measurements Utilizing an MRI Compatible Treadmill

Introduction

An overwhelming body of research supports maximal oxygen consumption (VO₂max) as an important measure of overall health and fitness. According to international governing bodies, such as the American College of Sports Medicine (ACSM), VO₂max is the number one measured predictor of all-cause mortality [9]. Increasing clinical interest in VO₂max and diagnostic exercise examination has led to many recent advances in technology and testing methods. There are many benefits to performance VO₂max testing for performance athletes. Similarly, clinical application of exercise testing continues to be valuable tool for health care professionals in diagnosis, prognosis, and treatment of disease.

Optimizing test diagnostic effectiveness, while decreasing invasiveness and costs are common challenges associated with clinical exercise testing practices. Current testing procedures have considerable diagnostic value with sensitivity ranging from 68-97% and specificity of 64-86% [10, 42, 46, 48-50]. However, current testing practices frequently require patients to undergo multiple tests for confirmed diagnoses. Reimbursement for diagnostic testing procedures has declined significantly in recent years [55].

Improvements in resolution and single test reliability are a necessary advancement in clinical diagnostic exercise testing.

Research breakthroughs in magnetic resonance imaging (MRI) techniques recently have resulted in enhanced interest and capacity for new exercise stress testing procedures. MRI, provides many diagnostic benefits including enhanced temporal, spatial, and contrast resolution without need for contrast injection exposing patients to ionizing radiation. MRI completely meets many requirements of a gold standard diagnostic imaging tool [16]. Developments particularly in functional cardiac magnetic resonance (CMR) imaging techniques have re-ignited interest in exercise stress imaging and diagnostics.

Clinical stress testing may be administered with or without exercise. Pharmacological stress testing, although utilized in some patient populations, provides no diagnostic benefit to the majority of ambulatory populations [55]. Physiological stress from exercise is superior and elicits greater demand on the heart and increases probability for achieving an ischemic threshold thus maximizing diagnostic benefits when compared to pharmacological stress testing. Development of MRI-compatible exercise equipment has produced an invaluable opportunity for advancement of diagnostic exercise testing.

Worldwide, the most common clinical exercise test modality utilized is the cycle ergometer. Numerous studies have reported production of higher VO_2max (5-20% increase) with weight bearing, running, versus weight supported, cycle ergometer, exercise [2, 18, 31, 40-42]. Evidence suggests treadmill exercise is a more effective tool for assessing maximum work capacity compared to the cycle ergometer. Current clinical

stress testing procedures rely heavily on predicted max heart rate and perception of exercise intensity to confirm maximal exertion. Unfortunately, predicted max heart rate estimates are notorious for their poor accuracy, especially in individuals who are greater than fifty years of age. Clinical diagnostic testing and patient populations, are disproportionately represented by individuals who are not well served by age predicted max heart rate estimation. Addition of oxygen consumption measurement (VO_2) to clinical diagnostic testing provides more information for diagnosis and would allow clinicians greater certainty when determining patients' maximal effort achievement.

To date there have been no published studies that utilize a MRI compatible treadmill to measure maximal oxygen consumption in conjunction with CMR imaging before and after exercise stress. The purpose of this study was to assess feasibility and validity of VO_2max measurement in an exercise lab versus an MRI suite using a MRI-compatible treadmill to induce maximum physiological stress prior to cardiac function imaging. VO_2max will be an accurate and valid measure when obtained in an exercise laboratory versus a clinical MRI exam room. Addition of VO_2max to CMR cardiac function measurement will be viable after quantifiable maximal exercise exertion is reached in recreationally trained healthy adults.

Methods

Subjects

Participants of this study were recruited from the Ohio State University community in Columbus, Ohio. Participant descriptors are illustrated in table 3.1.

Eligible participants were healthy, recreationally, trained individuals between the ages of 18 and 45 years old. All enrolled research subjects gave informed consent prior to participation. The study was approved by The Ohio State University Biomedical Institutional Review Board. In order to minimize the effect of any learning curve, eligible participants were required to have familiarity with performing a Bruce protocol VO_2max test. Individuals were excluded from this study if they did not fit within the American College of Sports Medicine's (ACSM) risk stratification criteria for maximal exercise testing as laid out in the ACSM Guidelines for Exercise Testing and Prescription, 9th edition.

Table 3.1. Participant Descriptors

	Lab 1 vs Lab 2 (N = 10)		Simultaneous Test (N = 7)	
	Mean $\pm$ SD	Range	Mean $\pm$ SD	Range
Age (yrs)	26.1 $\pm$ 5.7	21-37	26.1 $\pm$ 5.9	20-36
Height (in)	67.5 $\pm$ 3.8	63-74	69.0 $\pm$ 4.8	63-76
Weight (lbs)	151.9 $\pm$ 29.0	113-207	161.8 $\pm$ 32.1	125-201

Physical characteristics displayed above are those of consenting adults that participated in this research. The first group tested in different laboratories consisted of 5 males and 5 females. The second group tested using a simultaneous in-line set up consisted of 4 males and 3 females.

Design

The first arm of this study employed a random crossover design. All participants performed two continuous progressive graded exercise tests to volitional fatigue maximal oxygen consumption (VO_2max) was measured during two separate testing sessions in different settings. Each subject was randomly assigned to first test in either the exercise

laboratory (Lab 1) or the MRI suite (Lab 2). Cardiac magnetic resonance (CMR) imaging was performed to measure cardiac function at rest and after VO_2max exercise stress when tested in Lab 2. Total test duration was recorded at completion of the initial VO_2max testing session. Participants were encouraged to exercise to the same time end point during their second exercise test in order to eliminate differences in overall work load between test sessions.

Two separate locations, Lab 1 and Lab 2, were measured for validity and reproducibility during graded exercise testing. Oxygen consumption (VO_2), ventilation (Ve), respiratory exchange ratio (RER), fractional concentration of oxygen (FEO_2), carbon dioxide (FECO_2), and respiratory rate (RR) were compared between the two locations during time matched exercise tests in a group of, 10 healthy and recreationally trained athletes. Heart rate (HR) and Borg's rating of perceived exertion (RPE) were also utilized to compare physiological and participant perception of exercise stress during VO_2max testing between locations.

The second arm of this research addressed reliability of metabolic measurement. Respiratory data was collected during a single exercise test session by two automated gas analysis systems. Seven healthy, recreationally trained athletes completed a graded exercise test to volitional fatigue, while systems simultaneously collected metabolic data during exercise. Again, VO_2 , Ve , RER, FEO_2 , FECO_2 , and RR were compared. Secondary measures HR and RPE were also recorded.

Protocol and Equipment

Each participant from research arm I was tested using the Bruce graded exercise treadmill protocol in two independent testing sessions. Stages were 3 minutes in duration. Speed and grade of the treadmill were increased according to Bruce protocol standards. Criteria for achievement of maximal exertion during exercise were plateauing of oxygen consumption (VO_2), $\text{RER} \geq 1.1$, heart rate $\geq 95\%$ age-predicted max heart rate (APMHR), rating of perceived exertion (RPE) ≥ 17 , RR > 40 breaths per minute, and subject inability to continue. In all participants a minimum of three criteria, listed above, were met prior to completion for a valid VO_2max measurement. Blood lactate measures were not performed during this study due to MRI safety considerations. Metabolic data was sampled using 15 second averaging. The last 30 seconds of each completed submaximal stage as well as the final 30 seconds of exercise were averaged to determine VO_2 throughout exercise.

All VO_2max tests were conducted using ParvoMedics TrueOne 2400 systems. Both ParvoMedics TrueOne 2400's utilized an automated "mixing chamber" gas analysis system. Dell computers with Windows Vista operating system and ParvoMedics software were present in both of the metabolic carts. Despite being identical models, one TrueOne 2400 system was older than the other. Each system was in working order and flowmeter and gas analysis calibrated according to recommended manufacturer instructions prior to each use. Room air temperature, humidity, and barometric pressure were entered prior to calibration. Respiratory air passed through Hans Rudolph (Shawnee, KS, USA) 2700 two-way non-rebreathing valves, two saliva collector traps into a 35mm diameter

corrugated plastic tube. Air was filtered using a Creative Biomedics Inc (San Clemente, CA, USA) purple filter prior to being heated by a Hans Rudolph pneumotachometer and entering a 4 L mixing chamber. Gas was continuously sampled during exercise, through a 61 cm Nafion tube (Permapure, Toms River, NJ, USA), via paramagnetic oxygen analyzer (0-25% range with 0.1% accuracy) and an infrared carbon dioxide analyzer (0-10% range with 0.1% accuracy). TrueOne 2400 systems were turned on 30 minutes prior to testing in each lab. Heart rate data were collected in Lab 1 with Polar H7 Bluetooth Smart Heart Rate Sensor (Polar Electro Inc., NY, USA). MRI-compatible ECG was used to monitor and record heart rate during exercise in Lab 2.

Research Arm I: Separate Testing Session Set Up

Participants were tested with two different treadmills. Lab 1 featured a Trackmaster electronically driven motor treadmill. Lab 2 required a novel MRI-compatible hydraulically powered EXcmr treadmill be used. Lab 2 exercise tests were completed within a clinical MRI testing room, as such, precautions were taken to remove ferromagnetic items from the testing equipment within MRI magnetic field. Hans Rudolph non-rebreathing expiratory valve check was replaced with plastic components. Similarly, Hans Rudolph headgear was modified with nylon bolt, wing-nut replacements, and Velcro for participant, researcher, and technician safety. Similarly, TrueOne 2400 system cart was located in a safe control room during testing. Therefore rather than using a 6 foot long corrugated plastic tube as in Lab 1, an extended combination of one 9 foot and one 6 foot long 35mm diameter corrugated plastic tube was utilized to create a 15

foot long tube capable of allowing passage of expiratory gas from participant to metabolic cart in MRI operation safe control room.

Research Arm II: Simultaneous Testing Set Up

Simultaneous testing was performed in an exercise testing laboratory. Equipment from Lab 2, MRI suite was brought to the exercise testing laboratory. Two ParvoMedics TrueOne 2400 automated systems were assembled in-line as described by MacFarlane et al. 2013. One 15 foot long 35mm corrugated plastic tube was fed directly into both TrueOne 2400 systems. Two pneumotachometers were connected in-line with an 6cm (35mm diameter) corrugated plastic tube. Pneumotachometer order was switched after each test to prevent any potential ordering effect by having expiratory gases consistently pass through one pneumotachometer first. Flowmeter and gas calibration were completed simultaneously before each test according to manufacturer's instructions. Participants performed a Bruce protocol maximal exercise treadmill test to exhaustion while metabolic gas analysis was measured simultaneously with two automated TrueOne 2400 systems.

MRI Data Acquisition

Magnetic Resonance Imaging was completed using Siemens 1.5-T magnet, (MAGNETOM, Avanto, Siemens Healthcare, Germany). Left ventricle Cine images were acquired at rest and (~36 seconds) following maximal exercise stress. Transverse (10mm) slices of the heart were acquired using a 32 channel coil and saved for subsequent analysis. Field of view (FOV) was 285mm x 380mm. Matrix was set at 80 x 160 pixels; while temporal resolution was 44.6 with an acceleration rate of 4. Parallel

imaging was performed using TGRAPPA algorithm. End diastolic volume (EDV) and end systolic volume (ESV) were calculated from contours manually drawn around circumference of left ventricular lumen in resting and stress images using Argus ventricular analysis software (Siemens, Malvern, PA). Figure 3.1 depicts manually drawn contours for five transvers slices at end diastole and end systole. Cardiac function measures stroke volume (SV), left ventricle ejection fraction (LVEF), and cardiac output (CO) were assessed at rest and after maximal exercise stress based upon HR, EDV and ESV data. Post exercise heart rate was confirmed during image acquisition scanning using trigger time and image frames while participants were inside magnet bore.

Figure 3.1. Cardiac Function CMR Cine Images of Heart: Images of left ventricle at end diastole and end systole shown above acquired at rest and stress. Contours were manually drawn in five short-axis 10mm slices. End diastolic volume (EDV) and end systolic volume (ESV) were calculated using Argus ventricular analysis software (Siemens, Malvern, PA).

Statistical Analyses

All physical measures and metabolic data are reported as mean and standard deviation. To compare differences between group mean data from Lab 1, Lab 2, and corresponding ParvoMedics TrueOne 2400 systems percent difference and paired T-tests

were used. To determine if relationships between test variables were systemic or random, Lin's Concordance Correlation Coefficient was used to evaluate agreement between quantitative measurement methods. Bland-Altman analyses were completed to further compare parameters measured between different laboratories during separate testing sessions and to evaluate variability of individual metabolic carts during simultaneous in-line data collection. Statistical significance was set at $p \leq 0.05$.

Results

Figure 3.2. Comparison of mean VO_2 : 3.2A (left) illustrates differences between testing locations Lab 1 (Exercise Testing Lab) and Lab 2 (MRI Suite). Each bar represents mean VO_2 for group when tested in two different settings on separate occurrences less than 7 days apart. 3.2B (right) depicts differences between mean VO_2 measures when measured simultaneously with 2 systems during the same test session.

Rate of oxygen consumption is shown between locations shown in figure 3.2A .

During testing there was group mean discrepancy between VO_2 measures ranging from 1.3 to 2.5 ml/kg/min. Variability between test measures grew as exercise intensity

increased. The largest differences are seen during the stage 4 and 5 of the Bruce protocol. Percent difference during stages 4 and 5 when tested on separate days and in different locations was 5.23 and 4.99, respectively. As shown in figure 3.2B there were also differences when testing simultaneously with the same TrueOne 2400 units as shown in 3.2A. During simultaneous testing mean VO_2 measures there was a range of differences, 2.4 to 7.7 ml/kg/min. During simultaneous testing discrepancies between oxygen consumption rates were increased during stages 3 and 4, where percent difference was 11.9 and 16.3 respectively. Despite VO_2 values measured at submaximal exercise being more varied, $\text{VO}_{2\text{max}}$ values were on average 2.9 ml/kg/min (5.7%) different between the two TrueOne 2400 systems.

Metabolic variables, FEO_2 , FECO_2 , Ve , RR , and RER were recorded during testing to further assess viability of achieving $\text{VO}_{2\text{max}}$ while exercising. Heart rate and RPE were observed as secondary criteria. During the final 30 seconds of each test these variables were collected and compared using % Difference, paired T-tests, and Lin's Concordance Correlation Coefficient (ρ_c). The data are shown in table 3.2. There were significant differences ($p < 0.05$) between $\text{VO}_{2\text{max}}$, FEO_2 , and RER at maximal exertion when tested on separate days in different location as well as when simultaneously measured. Maximal heart rate achieved when testing in Lab 1 was significantly lower ($p = 0.01$) than measured in the same subject population when tested in Lab 2. Rating of perceived exertion (RPE) was not statistically different between testing laboratories; although there was a slight decrease in RPE given for Lab 2 compared to Lab1. FECO_2 , Ve , and RR at maximal exercise intensity were not statistically different.

Table 3.2 Metabolic Data at Maximal Exertion

A) Lab 1 versus Lab 2 comparison						
	Lab 1	Lab 2	% Difference	Paired T Test	ρ_c	95% LCL
VO ₂ max	47.6 ± 8.11	50.0 ± 10.7	4.99	0.033*	0.9142	0.8182†
FEO ₂ (%)	17.5 ± 0.48	17.1 ± 0.50	2.31	<0.01**	0.6581	0.3101
FECO ₂ (%)	4.1 ± 0.45	4.1 ± 0.57	0.00	0.535	0.8258	0.5677
Ve (L/min)	105.0 ± 24.0	109.1 ± 38.3	3.83	0.536	0.7935	0.5899
RR (bpm)	49.7 ± 11.6	48.9 ± 16.2	1.62	0.736	0.8598	0.6861
RER	1.24 ± 0.10	1.13 ± 0.06	9.28	<0.01**	0.3710	0.1355
Max HR (bpm)	187.0 ± 12.4	191.2 ± 12.2	2.22	0.01*	0.8830	0.7008
RPE	18.2 ± 1.03	17.5 ± 1.27	3.92	0.356	0.4137	-0.038
B) Simultaneous In-line Comparison						
	Lab 1 Cart	Lab 2 Cart	% Difference	Paired T Test	ρ_c	95% LCL
VO2max	49.4 ± 10.2	52.3 ± 10.3	5.70	<0.01*	0.9528	0.8666†
FEO ₂ (%)	17.3 ± 0.22	17.1 ± 0.27	1.16	<0.01**	0.7446	0.4423
FECO ₂ (%)	4.11 ± 0.18	4.14 ± 0.26	0.73	0.522	0.8647	0.6623
Ve (L/min)	98.6 ± 35.7	98.9 ± 35.1	0.30	0.610	0.9988	0.9952†
RR (bpm)	44.7 ± 7.17	45.3 ± 7.12	1.34	0.338	0.9780	0.9090†
RER	1.15 ± 0.05	1.10 ± 0.05	4.44	<0.01**	0.5228	0.1845

Values are presented as mean ± SD.

ρ_c = Lin's Concordance Correlation Coefficient

* Significant Difference p<0.05 ** Significant Difference p<0.01 † Interchangeable 95% LCL >0.75

Table 3.2A provides a comparison of metabolic data collected at maximal exertion when tested in two different settings. Table 3.2B displays data collected on two separate metabolic carts from a single graded exercise test session. Max HR and RPE were recorded during single test session with simultaneous in-line gas measurement. Group mean max HRmax was 190.4±7.07, RPEmax was 19.1±0.8

Lin's concordance correlation coefficient was used to determine agreement between testing methods. 95% Lower Confidence Limit (95% LCL) values were used to evaluate agreement. Measurements were considered interchangeable if 95% LCL was > 0.75 [56]. VO_2max was significantly different ($p = 0.033$) in when tested in different settings, 95% LCL was 0.8182. During simultaneous, in-line, testing VO_2max measures, despite being significantly different ($p < 0.01$), were in excellent agreement (0.8666). Other variables, Ve and RR 95% LCL values were 0.9952 and 0.9090 respectively. Poor agreement was shown in FEO_2 , RER , and RPE in both test separate and simultaneous experiments.

Bland-Altman analysis, shown in figure 3.3 was completed comparing VO_2max values when tested separately as well as simultaneously. Average VO_2 (ml/kg/min) was plotted against the difference between measured values. In 9 out of 10 participants VO_2max data collected when testing in separate locations falls well within 1.96 SD from the mean. Similarly, during simultaneous testing all 7 measures of VO_2max are shown within 1.96 SD. There is a noticeably larger difference range during separate location testing, approximately 2 fold greater than during simultaneous testing.

Figure 3.3. Agreement and Interchangability of Measures: Concordance Correlation Coefficient plot (3.3A, 3.3C) and Bland-Altman analysis comparison of VO₂max data, from 10 participants, observed in Lab 1 versus Lab 2 (3.3B) as well as for simultaneous data collection during single exercise session for 7 participants (3.3D)

Figure 3.4. Cardiac Function Measures Rest and Stress: Line plots 3.4A-F represent cardiac function measures acquired via MRI before and after exercise for 10 participants. Five CMR short axis Cine images were acquired of left ventricle. Images were analyzed using Argus computerized system. Contours were drawn manually for each 10mm slice. Left Ventricle End diastolic Volume (LVEDV) and Left Ventricle End Systolic Volume (LVESV) were computed in Argus ventricle analysis software. EF, SV, and CO were calculated from LVEDV, LVESV, and HR values.

MRI cardiac function measures of the heart are shown in figure 3.4. LVEDV and LVESV were made at rest and after peak exercise stress. LVEDV was unchanged ($p = 0.97$) after exercise, yet LVESV significantly decreased ($p < 0.01$) after exercise. Mean left ventricle ejection fraction (LVEF) was increased 65.2 ± 3.3 to 78.4 ± 4.8 . Cardiac function measures EF, SV, and CO were all significantly increased after exercise ($p < 0.01$). CMR computed Heart rate (HR) during scanning was also increased significantly after exercise. At maximal exercise intensity group mean HR were 191.2 ± 12.2 bpm. Mean 35.6 ± 3.8 seconds transition time after exercise during CMR scanning group average HR was 166.3 ± 20.2 bpm.

Discussion

The main finding of this study was that VO_2max exercise testing was feasible and valid when measured in a clinical MRI exam room (Lab 2), using a MRI-compatible treadmill compared to an exercise testing facility (Lab 1). Variability between two separate testing sessions in two different locations was within an acceptable range according to previous literature, ACSM, and manufacturer guidelines. All participants were tested via Bruce treadmill protocol to volitional fatigue. VO_2max rate of oxygen consumption measurement in an exercise laboratory compared to an MRI suite was slightly less ($< 2.5\text{ml/kg/min}$) and significantly different ($p < 0.033$) at maximum exercise. Lin's concordance correlation coefficient, 95% LCL, between values was 0.8182, considered interchangeable (> 0.75) [56]. Mean VO_2max measures collected in

the exercise laboratory were, on average, 4.99% lower than values measured in the MRI suite via MRI-compatible treadmill.

RER_{max} and HR_{max} values were significantly different (~ 0.01) between the two test locations. Maximum HR was measured higher (191.2 ± 12.2) in the MRI room compared to the exercise lab (187.0 ± 12.4). Mean max HR observed in the MRI room may indicate increased effort, decreased hydration status, or psychological factors such as anticipation of MRI scan. Bruce protocol was followed during time matched testing in each setting, therefore workloads were theoretically equal. Utilization of different treadmills may contribute to variance during set speed and grade matched workloads. Treadmill speed and grade calibrations performed showed that both treadmills used during testing were within manufacturer specifications for % error. Treadmills were nearly the same in actual versus displayed speed and grade measures.

Elevated, significantly different ($p < 0.01$) RER values were observed at maximum exertion in Lab 1 (1.24 ± 0.10) versus Lab 2 (1.13 ± 0.06), indicating an increase in VCO_2 expired. RER is commonly used to determine whether activity requires aerobic or anaerobic energy metabolism. Thus increases in RER may be caused by increases in exercise intensity and lactic acid production. Similarly, during simultaneous, in-line, testing, mean RER_{max} measures were higher (1.15 ± 0.05 vs. 1.10 ± 0.05) in the TrueOne 2400 system from Lab 1 compared to those measured by TrueOne 2400 system in Lab 2. This finding suggests differences in mean RER_{max} measures at max exercise may be due to metabolic cart inter-unit variability.

There were several necessary modifications required in order to safely measure VO_2max in the presence of MRI. Variables likely to have potential effects on measurement of metabolic variables, including VO_2 , were hose length and utilization of two separate TrueOne 2400 systems. Despite modifications compounding variables did not result in differences between VO_2max measures that were considered outside variability ranges published in previous studies, nor did they surpass reasonable limits set by ACSM and manufacturers' guidelines. Several research studies have shown that maximal exercise performance varies significantly day to day [34-37, 57]. National accreditation bodies such as ACSM accept a variance of approximately 4% (2-3 ml/kg/min) between testing sessions when variables are controlled, however there are studies that report individual VO_2max values that vary as much as 15 to 22% when tested during separate sessions [9, 34-36]. Differences in measured values during separate test sessions on different days may be due in large part to compounding variables such as nutrition, hydration status, motivation, psychological factors, and equipment error.

ParvoMedics equipment has been extensively studied for accuracy and reliability. In a study by Crouter et al. 2006, MedGraphics VO2000, and the ParvoMedics TrueOne 2400 were compared for reliability against the gold standard Douglas Bag method. Reliability of three VO_2 measurement systems was assessed between days via cycle ergometer exercise testing. MedGraphics VO2000 (CV 14.2-15.8%) was less reliable than DB (CV 5.3-6.0%) and the TrueOne 2400 (CV 4.7-5.7%) [37]. Macfarlane et al recently published a similar study in 2013 that tested the inter-unit variability of two consecutively manufactured ParvoMedics TrueOne 2400 systems. The results of this

study were a within subject mean coefficient of variation (CV) of ~4% and a mean absolute percentage error (APE) of ~6%, while the inter-unit error was CV ~1.5% and APE ~2.1% [38]. A 1982 study by Katch et al. reported, using 80 repeated VO_2max trials with Douglas Bags, within-subject variation to be 5.6% [39]. There is a large range presented within published data that suggests variation in VO_2 measures may be greater than expected. Nonetheless when in good working condition and calibrated correctly, <6% error is within a reasonable range for the ParvoMedics TrueOne 2400 platform.

Simultaneous in-line test data was collected in an effort to further understand the variability that resulted from testing between laboratories. Research arm II was intended to provide information about variability between testing performed using the same two TrueOne 2400 metabolic carts from research arm one was a result of differences associated with location and exercise session differences, inter-unit variability, or a combination of both. VO_2max tests were completed where in our two metabolic carts were tested simultaneously. During this simultaneous, in-line, testing described in Macfarlane et al. 2013, participants would breathe into one single 35mm corrugated plastic tube, yet VO_2 was measured by each TrueOne 2400 system during a single exercise test. During simultaneous measurement, variables thought to be contributors to error during separate test sessions were minimized or eliminated. Hose length, location, and treadmill were kept constant. Similarly, all mouth piece, valves, head gear, and physiological parameters were unchanged during simultaneous, in-line, VO_2max testing. Mean VO_2max values were approximately 2.9 ml/kg/min (5.7% different) higher when measured by the cart originally used during testing in the MRI suite. There was a

significant difference ($p < 0.01$) between the two metabolic cart measures. Lin's concordance correlation coefficient (0.8666) suggesting methods are in excellent agreement and would be interchangeable during simultaneous testing. Bland-Altman analysis was used to compare measures in both separate and simultaneous VO_2max testing. Bland-Altman analysis in separate test settings resulted in 9 out of 10 values being represented within 1.96 SD of the mean. Simultaneous, in-line, testing Bland-Altman analysis reveals 7 out of 7 values were within 1.96 SD of the mean.

Supine cardiac function measures via MRI data show significant ($p < 0.01$) increases in HR, EF, SV, and CO. Cardiac output was significantly elevated 35.6 ± 3.8 seconds after maximal exercise from 5.1 ± 1.0 l/min, at rest, to 16.4 ± 3.6 l/min, following exercise stress. Healthy individuals may reach cardiac output during maximal exercise of 15-20 L/min, while elite level athletes may achieve cardiac output rates of 30-40 L/min [2, 58]. After ~36 seconds following max exercise stress, cardiac output decreases with heart rate. Mean heart rate at maximum exercise was 191.2 ± 11.6 bpm, however during MRI scan mean HR had decreased to 166.3 ± 20.2 bpm (~86.9% HR_{max}). End systolic volume was significantly ($p < 0.01$) decreased (44.6 ± 10.8 ml) before and after exercise (27.9 ± 11.0 ml). Decreases in ESV are likely due to increases in contractility associated with exercise induced enhancement of sympathetic tone, venous return, and Frank-Starling mechanism. Stroke volume was increased (82.8 ± 16.6 ml) to (99.6 ± 22.5 ml) from rest to ~36 seconds post exercise. Similarly, LVEF was increased 65.2 ± 3.3 to 78.4 ± 4.8 further indicating an increase in contractility and efficiency within the left ventricle following max exercise.

Well trained endurance athletes have stroke volumes of approximately 100 ml at rest. The mean SV for participants in this study was slightly below that of trained athletes. This is attributed to cardiovascular fitness in study participants being representative of a recreationally trained, rather than elite athlete population. Cardiac output and stroke volume measures from this study align with normative data from healthy adults [2, 58]. Left ventricle end diastolic volume was unchanged before and after exercise stress in ten recreationally trained individuals. Cardiac function measures were within expected ranges for a healthy adult at rest and post VO_2max exercise test for a recreationally trained group of 10 healthy participants.

Limitations associated with this study include alterations or additions made to testing equipment for MRI safety. Treadmills used to compare in Lab 1 versus Lab 2 were different in make, model, and function since standard electronically driven motor treadmills would be unsafe. In a standard exercise laboratory hose length is limited to approximately 6 feet, while in order to safely measure VO_2 in an MRI setting hose length was 15 feet. Hose length was not increased in Lab 1 to match Lab 2 in order to compare measures during MRI- VO_2max testing versus a typical diagnostic or clinical VO_2max stress test set up.

Similarly, adaptations were made to head gear and valve check devices to remove ferromagnetic components. Headgear and valve check device changes were believed to have null effects on testing measures as function was not impacted by changes made. Variations in test set up or equipment were included in study methods knowingly. It is unrealistic to increase standard hose length to 15 feet for a clinical or diagnostic VO_2max

test when MRI is not present. Therefore, in this study we attempted to validate MRI-VO₂max testing when taking MRI precautions versus a typical set up. The data indicate there are negligible effects on accuracy and feasibility of VO₂max measurement when testing via an MRI-compatible treadmill in a clinical MRI suite. More research is required to test more diverse healthy and patient populations to determine if MRI-VO₂max stress testing may be a viable tool available to clinicians for diagnostic and prognostic information.

Seventeen total participants were included in this study. Ten healthy recreationally trained participants were tested in separate locations on different days, while seven were tested using a simultaneous two cart set up. Research participant eligible for this study were healthy recreationally trained adults. This sample size could have been expanded to include a more diverse population including different ages, fitness, and health classifications.

Chapter 4: Conclusion

Maximal oxygen consumption is an important indicator of cardiorespiratory health. VO_2max has been recognized as the number one predictor of all-cause mortality [6-9]. Although underutilized, there is a great deal of potential for use of VO_2max in a patient based health care setting. Recent advances in technology and diagnostic imaging tools such as magnetic resonance imaging have reignited interest in exercise stress imaging techniques. VO_2max measurement may offer more vital physiological information for health care professionals during diagnosis and prognosis of patient.

Current testing and patient care standards rely on a myriad of options for diagnosis. There are a number of exercise and pharmacologically derived stress testing procedures that can be administered, yet the goal remains the same to collect information that will result in a clear diagnosis for proper treatment. It is important that the appropriate test be selected for accurate results. As reimbursement decreases for diagnostic stress testing it increasingly becomes critical that test methods be as informative as possible. Combination techniques are commonly used to provide more efficient information so as to not increase the amount of time and finances unnecessarily from testing that offers unconfirmed diagnoses.

According to the American College of Cardiology, American Heart Association, and other governing bodies on heart health, there is no benefit to using pharmacological

stress testing in ambulatory patients capable of exercise. Physiological exercise stress is superior to pharmacological stress because there is a greater tendency for exercise stress to produce maximal working capacity of the cardiovascular system. Thus there is a great need for techniques that offer exercise stress testing in conjunction with advanced imaging. MRI has been shown to provide key characteristics of a gold standard imaging technique such as high temporal, spatial, and contrast resolution [16]. Recent creation of an MRI-compatible treadmill presents a host of opportunities for clinical MRI assessment. In this research VO₂max testing was combined with cardiac magnetic resonance in order to assess the feasibility, accuracy, and validity of the measures for potential future use in clinics.

Measurement of VO₂max and cardiac function in MRI setting was feasible in a group of ten recreationally trained individuals. Comparison of VO₂max between a typical exercise stress testing lab and the MRI suite showed that variability was within 4-6% accepted range for separate testing within subjects. All participants were able to achieve maximal physical exertion via MRI-compatible treadmill. CMR cardiac function measures also indicated participants were able achieve maximal exercise stress. Simultaneous testing of seven recreationally trained individuals was completed to measure inter-unit reliability. There were no differences in results when VO₂max was measured in two separate locations versus during a simultaneous single exercise session. We believe that MRI-VO₂max testing is a valid and accurate assessment of cardiorespiratory health. VO₂max testing in conjunction with CMR assessment of cardiac function may provide enhanced diagnostic and prognostic information for

clinicians in the future. More research will need to be done to confirm these findings in a broad range of healthy aged participants and patients alike.

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