

**HEART RATE VARIABILITY AS A NON-INVASIVE BIOMARKER OF
SYMPATHO-VAGAL INTERACTION AND DETERMINANT OF
PHYSIOLOGIC THRESHOLDS**

by

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DISSERTATION

Submitted to the Graduate School

of Wayne State University,

Detroit, Michigan

in partial fulfillment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

2008

**MAJOR: EDUCATIONAL EVALUATION
& RESEARCH (Physiology)**

Approved by:

Advisor

Date

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DEDICATION

For their continual encouragement and support throughout my education, this work belongs to my wonderful wife Nayiri and my parents Jan and David – without them, I would not have made it this far. I am most grateful to the Lord, who has blessed me in many ways throughout these years.

ACKNOWLEDGEMENTS

The direction and guidance I have received from each member of my committee is greatly appreciated. The professionalism and expertise provided by Dr. Randall Gretebeck and Dr. Hermann-J. Engels is without a doubt, the reason I have enjoyed my time at Wayne State University. I have truly benefited from their wisdom. Dr. Kimberlee Gretebeck has offered much insight of great importance; and Dr. Shlomo Sawilowsky, who agreed without hesitation to accept me as a graduate student with the passing of my initial advisor, the late Dr. Donald Marcotte, has offered his skills to help me along the way. I am thankful for each committee member and their willingness to share with me their wealth of knowledge.

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CHAPTER 1 INTRODUCTION

Metabolic Measures

The traditional physiological parameter used to predict endurance performance is the maximum oxygen uptake (VO_{2max}) (Mitchell, Sproule, & Chapman, 1957; Saltin & Astrand, 1967). Clinically based graded exercise treadmill tests which do not measure oxygen consumption (VO_2) typically calculate results from estimation equations utilizing test time or power output (American College of Sports Medicine, 1995a), rather than base functional capacity on actual measures of VO_2 (Pollock & Willmore, 1990). It is well established that in healthy groups, these treadmill estimation equations can accurately predict VO_2 , however, the calculations have been found to overestimate VO_2 in participants with other disorders such as coronary artery disease (Foster et al., 1984; Miller, Jago, Ribisl, & Boone, 1981; Sullivan & McKirnan, 1984), and may even overestimate to a large degree (Roy, Grove, & Christie, 1992). For this reason, laboratory metabolic testing remains the gold standard.

Aside from clinical treadmill tests, when studying other exercise testing modalities, there is even less research available regarding the ability to estimate VO_2 in compromised and/or unhealthy (cancer, cardiovascular disease, coronary artery disease, diabetes, hypertension) samples (Milani, Fernhall, & Manfredi, 1996). Cycle ergometry tests have, however, become more popular in research areas concentrating on cardiac, autonomic nervous system, and vagal effects on measurements of heart rate variability (HRV) (Blain, Meste, Bouchard, & Bermon, 2005; Cottin et al., 2006; Cottin et al., 2004; Tulppo, Makikallo, Seppanen, Laukkanen, & Huikuri, 1998). But the overwhelming majority of these tests are conducted on elite level athletes, with little research in samples

of the normal-to-diseased range. Evidence does suggest that non-weight bearing exercise modalities such as cycle ergometry result in little to no difference between estimated and measured VO_2 (Hamm, Stull, Nelson, & Rysdahl, 1993; Mertens, Kavanagh, Qureshi, & Shephard, 1993), which implies that cycle ergometry may be a convenient and preferred testing modality in both healthy and disease affected samples.

Laboratory Measures: Lactate Threshold

In addition to measurements of VO_2 , some authors have suggested other parameters, particularly the blood lactate (BLa) response to exercise, as important indicators of endurance performance (Farrell, Wilmore, Coyle, Billing, & Costill, 1979; Weltman et al., 1990), and stress the importance of understanding the lactate threshold (LT) as a key variable in the field of exercise physiology (Allen, Seals, Hurley, Ehsani, & Hagberg, 1985; Coyle, Coggan, Hopper, & Walters, 1988; Farrell et al., 1979; Weltman et al., 1989). Lactate threshold is the highest exercise intensity attained prior to an elevation in BLa is observed (Hoogeveen & Schep, 1997), and is detected by a marked increase in BLa concentration along with an increased carbon dioxide release because of the need to rapidly buffer lactic acid by bicarbonate in the lactic acid producing muscles (Moriguchi, Tomoda, & Ichimura, 2004).

Excessive lactate production is associated with a decrease in pH, which is then buffered by bicarbonate, resulting in an increase in blood partial pressure of carbon dioxide. The brain is then stimulated by chemoreceptors, which increase ventilation, returning partial pressure of carbon dioxide to normal. Because this lactate accumulation in the blood causes an increase in ventilation, LT presents a close relationship with another common measurement, ventilatory threshold (VT) (Dickhuth et al., 1999; Myers

& Ashley, 1997), the point at which pulmonary ventilation increases disproportionately in its relationship to oxygen consumption during exercise. Previous studies have indicated that, in incremental exercise tests, the gas exchanged in VT is only slightly below or no different from LT (Chicharro, Perez, Vaquero, Lucia, & Legido, 1997), suggesting the mechanism responsible for VT is vagal modulation of breathing, replaced by sympathetic control. Interestingly, HRV is under the same type of control system, and therefore, it may be possible to detect a similar threshold by examining changes in HRV during progressive exercise.

Laboratory Measures: Ventilatory Threshold

Ventilatory threshold is the point at which pulmonary ventilation increases disproportionately in its relationship to oxygen consumption during exercise (McArdle, Katch, & Katch, 2001). Because VO_{2max} is the traditional physiological parameter used to predict endurance performance (Mitchell et al., 1957; Saltin & Astrand, 1967), use of VT has gained widespread recognition (Blain, Meste, Bouchard et al., 2005; Cottin et al., 2006; Cottin et al., 2007). Lactate threshold is the most commonly accepted marker for cardiac transplant study participants, but research by Brubaker et al. demonstrated the use of VT (instead of LT) to determine exercise training intensity for cardiac transplant patients. The study showed that VT may be used as an indicator of LT in cardiac transplant patients and is within a range acceptable for clinical application (Brubaker, 1993). The use of ventilatory parameters is promising, but there is a need for further, more thorough investigation regarding VT measurement in diseased groups.

Laboratory Measures: Heart Rate Variability

Heart rate variability is a measure of the beat-to-beat variation in heart rate (HR) and the time between each heart beat (Alonso et al., 1998). The measure of HRV has been used at rest as a non-invasive tool for the assessment of cardiac autonomic control (Bluzaitė, Brazdžionyte, Zaliūnas, Rickli, & Ammann, 2006; Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology, 1996; Tsuji et al., 1996), and continues to undergo investigation during exercise, when important neural changes take place. Heart rate variability decreases under situations of emotional and physical stress and increases with rest while other changes in HRV occur with age, high insulin levels, reduced baroreflex sensitivity, rapid and shallow breathing, smoking, atherosclerosis, and diabetic autonomic neuropathy (Dekker, Crow, & Folsom, 2000). Heart rate variability is mainly vagally mediated (Karemaker & Lie, 2000) and it has been suggested that changes in HRV at higher intensities of exercise are due to a reduction in the vagal activity to the heart (Warren, Jaffe, Wraa, & Stebbins, 1997), specifically a decrease in HRV during exercise phases when heart rate increment is determined mainly due to vagal withdrawal (Chiou & Zipes, 1998). The vagus nerve controls HR when the parasympathetic nervous system dominates at rest and during periods of low physical activity. A possible cause for lower HRV that is manifested in disease is an increased dominance of the sympathetic nervous system and its influences on HR via the effects on sinoatrial node automaticity. This sympathetic dominance of heartbeat may coincide with vagal withdrawal, resulting in a higher HR and lower HRV.

Various physiological conditions, especially the presence of disease, obesity, fitness level, physical stress and intense physical activity, influence both the

parasympathetic nervous system and sympathetic nervous system affecting HR. Sympathetic dominance of heartbeat occurs at vagal withdrawal, when the vagus nerve withdraws its control of HR and the sinoatrial node and baroreceptors take control of HR. Vagal modulation of HR generally disappears at 50-60% of VO_{2max} (Tulppo et al., 1998), which is also the point at which there is an onset of blood lactate accumulation, causing an increase in ventilation and carbon dioxide excretion. The physiological changes associated with VT and LT are metabolic acidosis, impaired muscle contraction, hyperventilation, and altered oxygen kinetics (Gaskill et al., 2001). It has been suggested the mechanism responsible for VT is vagal modulation of breathing, replaced by sympathetic control (Tulppo, Makikallio, Takala, Seppanen, & Huikuri, 1996). Interestingly, HRV is under the same type of control system, and therefore, it may be possible to detect a similar threshold by examining changes in HRV during progressive exercise.

The objective of this dissertation is to determine if a heart rate variability threshold (HRVT) exists during exercise. If so, can this new, non-invasive measurement be used to identify other important physiological thresholds such as the ventilatory and lactate thresholds? There are many metabolic studies performed on normal, healthy participants under controlled laboratory conditions. But if a HRVT exists, will this measurement produce similar results under circumstances known to affect physiological parameters (pharmacological intervention) and in novel samples (obese, breast cancer survivors, stage I, II, or IIIA cancer, free of recurrence) for the detection of thresholds? Understanding the measurements of HRV and implementing the results appropriately will provide a scientific foundation for individual prescription of physical activity.

The assumption of this dissertation is that a non-invasive biomarker, HRV, does exist and can be used for the detection of physiological thresholds (VT, LT, HRVT) in normal, healthy participants; normal, healthy participants under the influence of caffeine; and obese, African American breast cancer survivors.

A limitation when estimating sympathetic domination of the autonomic nerve system by time domain indices is that the decreasing values of standard deviation (SD), mean successive difference (MSD), and coefficient of variation (CV) do not directly correspond to the increase in the autonomic nerve activity itself; rather they correspond directly to the modulation of sympathetic and vagal activities. The magnitude of vagal activity is directly related to a specific physical situation, e.g., increasing workload, but the modulation of the vagal activity shows only the rate of change in the vagal activity. Hibino et al. points out that “in potentially non-physiologic conditions, such as when parasympathetic nerve activity is maximally stimulated, e.g., when blood pressure is increased by phenylephrine (Cerati & Schwartz, 1991), the modulation of vagal activity would disappear” (p. 1425), consequently SD, MSD, and CV would also decrease to minimal levels (Hibino, Moritani, Kawada, & Fushiki, 1997). Malik et al. points out that only under standard physiologic conditions can the modulation of vagal activity, which is measured as SD, MSD, and CV in this study, be used to a certain degree as an estimator of that activity. Under potentially non-physiologic conditions, however, the relation between SD, MSD, and CV and the degree of vagal tone may not have the same fundamental value (Malik & Camm, 1993). The impact of non-physiologic or pharmacologic influenced alterations in sympathetic/vagal interactions will require further investigation.

CHAPTER 2 REVIEW OF LITERATURE

Autonomic Nervous System & Vagal Activity

The word “vagus” is derived from Latin, meaning, “wandering.” This term is fitting, as the vagus nerve wanders from the brainstem to the splenic flexure of the colon. The vagus nerve consists of five different components, each with distinct functions: cranial motor (special visceral efferent), visceral motor (general visceral efferent), visceral sensory (general visceral afferent), general sensory (general somatic afferent), special sensory (special afferent) ("Taber's Cyclopedic Medical Dictionary," 1997). Efferent fibers make up the parasympathetic (secretomotor) component of the vagus nerve, which innervate the smooth muscle and glands of the pharynx, larynx, and thoracic and abdominal viscera down to the splenic flexure ("Taber's Cyclopedic Medical Dictionary," 1997). In general, parasympathetic stimulation leads to increased secretion from glands and smooth muscle contraction. Parasympathetic stimulation slows HR, stimulates increased bronchiolar secretions and bronchoconstriction in the lungs, and stimulates increased secretions and motility in the gastrointestinal tract. These housekeeping effects are often referred to as the “rest and digest” portion of the nervous system.

The MONA LISA hypothesis, “Most Obesities kNown Are Low In Sympathetic Activity” put forward by Bray suggests an association between obesity and the reduced activity of the thermogenic component of the sympathetic nervous system (Bray, 1991). Regular physical activity and exercise training have a positive effect on the autonomic nervous system, so conversely, it has been established that increases in exercise intensity cause a significant withdrawal of cardiac vagal activity (Arai et al., 1989; Dixon,

Kamath, McCartney, & Fallen, 1992), but a decline in vagal tone has been linked to coronary heart disease and sudden cardiac death. Both experimental (Billman & Hoskins, 1989; Collins & Billman, 1989) and clinical (Kleiger, Miller, Bigger, & Moss, 1987) studies have revealed that participants with large decreases in parasympathetic tone (and/or an increase in sympathetic tone) following a myocardial infarction are at greatest risk of suffering from sudden cardiac death. It follows then, that exercise should be prescribed at intensities which maintain cardiac vagal activity, to help decrease the risk of sudden cardiac death during exercise, and for individuals to reap the benefits.

A strong likelihood exists that previously obese participants who have displayed a diminished activity of the autonomic nervous system, can enhance their autonomic nervous system activity to higher levels with regular physical activity (Amano, Kanda, Ue, & Moritani, 2001). Energy metabolism is influenced by the autonomic nervous system, and a change or diminution in sympathetic nervous system activity per se is believed to contribute to the pathogenesis of obesity (Bray, 1991; Peterson et al., 1988). Nishijima et al. recommends that exercise prescription should take into account sympatho-vagal activity in individuals who show a depressed activity of the autonomic nervous system, e.g. individuals who are obese or have diabetes (Nishijima et al., 2002).

A study demonstrating a decrease in cardiac sympatho-vagal activity in obese individuals indicated that body mass index (BMI) was negatively correlated with the HRV spectral results of that study (Petretta et al., 1995). It has also been observed that RR interval variability in obese women is smaller when compared with age-matched, non-obese women – mainly due to suppressed cardiac parasympathetic activity (Zahorska-Markiewicz, Kuagowska, Kvcio, & Mariusz, 1993). It has therefore been

proposed that obese individuals who are more likely to possess co-morbidities such as cardiac arrhythmia, diabetes, hyperlipidemia, and hypertension, follow an exercise prescription that takes into consideration sympatho-vagal activity as well as reduced autonomic nervous system activity (Shibata, Moritani, Miyawaki, Hayashi, & Nakao, 2002).

According to Blain et al., when increases in ventilation occur during intense exercise, it leads to a persistence of respiratory sinus arrhythmia (Blain, Meste, & Bermon, 2005). Their group studied sedentary, healthy men during a graded, maximal exercise test where measurements of instantaneous respiratory sinus arrhythmia frequency and instantaneous respiratory sinus arrhythmia amplitude were performed on the data. Then, the influences of different ventilation regimens (changes in tidal volume and respiratory frequency) on instantaneous respiratory sinus arrhythmia amplitude were tested during submaximal (70% peak oxygen consumption) exercise bouts. Their results indicate that respiratory sinus arrhythmia persists for all exercise intensities and increases during the highest intensities. Its persistence and increase are strongly linked to both the frequency and degree of lung inflation, which suggests a mechanical influence of breathing on respiratory sinus arrhythmia.

In a study examining determinants of exercise intensity based on cardiac vagal activity for obese individuals, Shibata et al. suggests it is possible to determine exercise intensity based on cardiac vagal withdrawal (Shibata et al., 2002). Shibata further recommends that exercise prescription based on vagal withdrawal thresholds allows for safe exercise intensities in obese individuals with higher risk factors for other complications. Matsumoto et al. contends that an association between obesity and a

relative or absolute reduction in the activity of the thermogenic component of the sympathetic nervous system exists (Matsumoto et al., 2001; Matsumoto et al., 2000; Matsumoto et al., 1999). Moritani et al. has shown that when compared with age-matched healthy participants, diabetic patients display less HRV, mainly due to a depression of activity in the cardiac parasympathetic nerve supply (Moritani, Hayashi, Shinohara, Mimasa, & Shibata, 1993).

Standard Measurements in Exercise Physiology

Primary prevention, especially in the form of physical activity and regular exercise, is of the utmost importance given that secondary and tertiary prevention approaches have not been sufficient against the epidemic rise in the incidence of coronary heart disease, type 2 diabetes, obesity, and other modern diseases (Booth, Gordon, Carlson, & Hamilton, 2000). There are many well-established measurements in the determination of cardiovascular fitness in the field of exercise physiology including LT, VT, VO_2 , HRV, HR, and respiratory exchange ratio (RER) – all of which have a role in exercise prescription, cardiovascular health, and the prevention of disease.

Without regular and proper exercise, obesity can result, where comorbidities include hypertension, diabetes, and an increased risk of cerebral and vascular diseases (Bray, 1985; Kissebah, Freedman, & Peiris, 1989; Manson, Willett, & Stampfer, 1995), medical complications that have a greater association with abdominal visceral fat than subcutaneous fat (Ducimetiere, Richard, & Cambien, 1986; Larson et al., 1984). Provided there are no contraindications, exercise training may be recommended to obese groups as a means to decrease abdominal visceral fat and improve general health (Shibata et al., 2002). Determining exercise intensity is of great importance for proper exercise

prescription, where initial exercise intensity is typically 60-70% of a healthy adults maximal aerobic capacity, and approximately 40-60% for adults with a lower aerobic capacity (American College of Sports Medicine, 1990, 1995b).

Standard Measurements in Exercise Physiology: Lactate Threshold

The model of muscle contraction occurring without the need of a continual oxygen supply may have been proposed as early as 1871 (Hermann, 1871). In the early 1900s, researchers proposed that lactate in the blood stimulated respiration during high-intensity exercise (Douglas & Haldane, 1909) and that it may have served to actually stimulate muscle contraction, and that oxygen was utilized by the body to remove the lactate, once it formed (Hill, 1911, 1912, 1913; Meyerhof, 1912a, 1912b). An association between exercise intensity, lactate production, metabolic acidosis, and bicarbonate buffering was soon established in several laboratories (Barr & Himwich, 1923; Bock, Dill, & Hurxthal, 1927; Douglas, 1927; Herbst, 1930; Hill, Long, & Lupton, 1924; Owles, 1930) where at one point, it was proposed (and widely accepted) that during exercise the build up of lactate in the blood reached a concentration that coincided with an inadequate oxygen supply unable to keep up with the energy requirements of the working muscle. Eventually, Wasserman et al. proposed that a threshold exists where certain physiological events occur: oxygen requirements by working muscles exceed the ability of the cardiopulmonary system to supply it; there is an increase in anaerobic metabolism; and lactate is formed in the working muscle (Wasserman & McIlroy, 1964). Myers et al. points out that lactate is the product of, not the cause of, muscle contraction (Myers & Ashley, 1997). It is now established, via isotopic tracers, that lactate production is not reliant upon anaerobiosis, and lactate is produced in muscles regardless

of oxygen supply (Brooks, 1991). Additionally, the concept that a sharp rise in BLa, often termed the onset of blood lactate accumulation, is indicative of muscles switching to an anaerobic mode is the center of much debate (Brooks, 1991; Katz & Sahlin, 1990; Stainsby & Brooks, 1990; Wasserman, Beaver, & Whipp, 1990).

The link between exercise intensity, lactate appearance, metabolic acidosis, and bicarbonate buffering has been well documented (Barr & Himwich, 1923; Bock et al., 1927; Douglas, 1927; Herbst, 1930; Hill et al., 1924; Hollman, 1985; Owles, 1930). The association between oxygen availability and BLa concentration has been proposed in studies which concluded that an increase in exercise training equates a decrease in BLa concentration during exercise (Holloszy & Coyle, 1984; MacRae, Dennis, Bosch, & Noakes, 1992), or that a decrease in cardiac output equates an increase in BLa concentration (Myers & Froelicher, 1991; Sullivan, Green, & Cobb, 1990; Weber, Kinasewitz, Janicki, & Fishman, 1982). Research supports the argument that lactate can be created under aerobic conditions (Brooks, 1991; Connett, Gayeski, & Honig, 1984), which contradicts previous beliefs that lactate production was exclusively dependent upon oxygen availability.

The field of exercise physiology has utilized isotopic tracer technology (Stanley, Wisneski, Gertz, Neese, & Brooks, 1988) thereby allowing lactate to be considered a substrate, rather than simply a byproduct with toxic effects (Brooks, 1991), revealing that working skeletal muscle both produce and consume lactate. It has been supported that this consumption can also occur in other tissue as well (Brooks, 1985, 1991). Lactate has been shown to form even in resting muscles, and during exercise its production and removal have been highly correlated to the metabolic rate (Connett et al., 1984).

Standard Measurements in Exercise Physiology: Ventilatory Threshold

Myers et al. (Myers & Ashley, 1997) illustrates the point that there has been a long evolution of measurements for detecting VT, some of which include the following: (1) an increase in RER; (2) an abrupt increase in the fraction of expired oxygen; (3) a nonlinear increase in ventilation; (4) a nonlinear increase in carbon dioxide production; (5) an increase in end-tidal oxygen partial pressure; and (6) the beginning of a systemic increase in the ventilatory equivalent for oxygen (V_E/VO_2) without an increase in the ventilatory equivalent for carbon dioxide (V_E/VCO_2) (Beaver, Wasserman, & Whipp, 1985; Caiozzo et al., 1982; Conconi, Ferrari, Ziglio, Droghetti, & Codeca, 1982; Davis, Vodak, Wilmore, Vodak, & Kurtz, 1976; Dickstein, Barvik, Aarsland, Snapinn, & Karlsson, 1990; Dickstein, Barvik, Aarsland, Snapinn, & Millerhagen, 1990; Dwyer & Bybee, 1983; Heck et al., 1985; Naimark, Wasserman, & McIlroy, 1964; Reinhard, Muller, & Schmulling, 1979; Shimizu et al., 1991; Sullivan et al., 1984; Wasserman et al., 1990; Wasserman & McIlroy, 1964; Wasserman & Whipp, 1975). There has been much debate regarding which of the determining criterion for VT equate a superior result, and the standout method which is widely accepted was defined by Beaver et al. (Beaver, Wasserman, & Whipp, 1986) and is known as the “V-slope.” In essence, it is the point where the slope of the VCO_2 and VO_2 curve become 1.0. Theoretically, this point is the most reliable as Myers and Ashely point out it is solely dependent on “the bicarbonate buffering response to lactate, and is independent of respiratory chemoreceptor sensitivity” (p. 791), rendering it the true ventilatory response to exercise (Myers & Ashley, 1997). This technique is extremely reproducible as it removes observer bias from

the measurement, and the resulting inflection point is not influenced by the specific method chosen to analyze the data.

Lactate is ever-present in the body and is constantly being produced and removed by working muscles and other tissues. This continual process occurs even at times of rest, and under both aerobic and anaerobic conditions. Blood lactate concentration is determined by the rate of production versus the rate of removal (via buffering or oxidation in other fibers). An increase in ventilation occurs when the BL_a accumulation in the blood reaches a point in which it cannot be cleared by tissues – a key representation of the VT. Physiologically, it is at this lactate accumulation point where a hindrance of the skeletal muscles ability to do work is also observed. Myers and Ashely state that metabolic acidosis, impaired muscle contraction, hyperventilation, and altered oxygen kinetics are known to occur here (Myers & Ashley, 1997). Exercise, specifically endurance training, demonstrates a delay in BL_a accumulation (resulting in a shift to a higher percentage of VO_{2max}) – which is often used as a precise predictor of performance in athletes. These measurements of BL_a and the valuable relationship they have with ventilatory changes during exercise provide helpful and functional relevance clinically, and in the field of exercise physiology.

Blain et al. studied both sedentary participants and endurance athletes on a graded, maximal cycle ergometry test to see whether VTs could be assessed using time varying analysis of respiratory sinus arrhythmia frequency (Blain, Meste, Bouchard et al., 2005). Two VTs were determined from the time course curves of ventilation and ventilatory equivalents for oxygen and carbon dioxide. Respiratory sinus arrhythmia frequency correlated well with respiratory frequency ($r = 0.96, p < 0.01$). In the majority

of participants, two successive non-linear increases were determined in respiratory sinus arrhythmia frequency, defining the first respiratory- and second respiratory-thresholds. These two thresholds were not significantly different from and closely related to the first VT ($r = 0.99$, $p < 0.001$) and the second VT ($r = 0.99$, $p < 0.001$) when expressed as a function of power. The study revealed significant differences ($p < 0.04$) between the athlete and sedentary groups when the first respiratory- and second respiratory-thresholds were expressed in terms of absolute and relative power and percentage of maximal aerobic power. The study revealed that dynamic analysis of respiratory sinus arrhythmia frequency provides a useful tool for identifying VTs during graded and maximal exercise test in sedentary participants and athletes.

Standard Measurements in Exercise Physiology: Oxygen Consumption

Exercise intensity is generally determined by a percentage of an individual's maximal aerobic capacity, as measured by VO_{2max} ; the onset of anaerobic metabolism, as measured by the RER, where the net output of carbon dioxide is compared to the simultaneous net uptake of oxygen at a particular moment in time; the onset of blood lactate, as determined by BLa production outpacing lactate clearance in working skeletal muscles; and/or VT, as evaluated by metabolic and respiratory responses during exercise.

Standard Measurements in Exercise Physiology: Heart Rate Variability

The measure of HRV has been used at rest as a non-invasive tool for the assessment of cardiac autonomic control (Bluzaitė et al., 2006; Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology, 1996; Tsuji et al., 1996), and is a measure of the beat-to-beat variation in HR and the time between each heart beat (Alonso et al., 1998). A component of

cardiac autonomic balance is the parasympathetic modulation of HR (a.k.a., the vagal modulation of HR). If HRV is to be utilized in risk stratification or to evaluate the effectiveness of an intervention, it must be reproducible (De Meersman & Stein, 2007). Gerritsen et al. demonstrated this moderate to high stability, and recommended a standardization of measurement conditions, stressing time of day, in an effort to eliminate diurnal rhythms (Gerritsen et al., 2003).

There are a variety of indices that have been used to assess HRV, which can be divided into 2 major categories: time domain indexes and frequency domain indexes. Time domain indexes such as SD, CV, and MSD which is the mean absolute difference between consecutive RR intervals, have been shown to correlate strongly with vagal tone just as frequency domain indexes such as the high-frequency component calculated by autoregressive spectrum analysis and fast Fourier transform (Hayano et al., 1991). Time domain indexes evaluate the overall magnitude of HRV using statistics, for instance the SD of the RR interval (Ewing, Borsey, Bellavere, & Clarke, 1981; Kleiger et al., 1987; Vybiral, Bryg, Maddens, & Borden, 1989), while frequency domain indexes evaluate the magnitude of individual components of the HR power spectrum (Akselrod et al., 1985; Akselrod et al., 1981; Furlan et al., 1990; Hayano, Sakakibara, Yamada, Kamiya et al., 1990; Hayano, Sakakibara, Yamada, Ohte et al., 1990; Lipsitz, Mietus, Moody, & Goldberger, 1990; Myers et al., 1986; Pagani et al., 1986; Pomeranz et al., 1985; Saul et al., 1988).

Hayano et al. examined the correlations of 11 indices of HRV in a pharmacological test to determine vagal tone in supine participants (Hayano et al., 1991). After sympathetic influences by intravenous propranolol were eliminated, RR interval

variability was measured for 10 minutes under controlled respiration (0.25 Hz), and cardiac vagal tone was determined as the decrease in mean RR interval following complete vagal blockade with atropine. Time domain indices (SD, CV, and MSD) demonstrated strong correlations with vagal tone ($r = 0.87, 0.81$ and 0.92 , respectively; $p < 0.001$ for all). The same was true for frequency domain indices for the high-frequency (0.25 Hz) component calculated both by autoregressive spectrum analysis (square root of power and coefficient of component variance) and by fast Fourier transform (mean amplitude) ($r = 0.91, 0.85$ and 0.86 , respectively; $p < 0.0001$ for all). Their results indicated that most of the time- and frequency-domain analyses in use provide an accurate and common measure of cardiac vagal tone at rest. Additionally, the high-frequency modulation of HRV has been accepted as a marker of the vagal modulation of HR (De Meersman & Stein, 2007).

The prognostic significance of HRV at rest has been well established, its potential usefulness under exercise-induced measurements however, have not been fully investigated. Dewey et al. examined time- and frequency-domain indices during exercise treadmill testing revealing that a greater percentage of high-frequency power, lower percentage of low-frequency power, and lower ratio of low-frequency to high-frequency during the recovery phase of exercise testing were significantly related to increased risks of cardiovascular death (Dewey et al., 2007). Dewey concluded that exercise-induced HRV variables during and after clinical exercise testing are excellent predictors both cardiovascular and all-cause mortality.

The feasibility of utilizing HRV to assess VT in athletes has been demonstrated in a study by Cottin et al. where eleven well-trained participants performed an incremental

exhaustive test on a cycle ergometer (Cottin et al., 2006). Short-term Fourier transform analysis was applied to RR interval time series in order to calculate the high-frequency HRV energy and high-frequency peak vs. power stages. When expressed as a function of power, the HF thresholds were respectively correlated with the first and second VTs (both $p < 0.001$). This confirmed that VT can be determined from RR intervals using HRV time-frequency analysis in healthy athletes (Cottin et al., 2006).

In another study by Cottin et al., it was examined whether VTs could be determined using HRV analysis (Cottin et al., 2007). This study was conducted with twelve professional soccer players who performed an incremental exhaustive running test on a track. They used the ventilatory equivalent method to assess the two VTs, and also assessed VTs by the instantaneous components of respiratory sinus arrhythmia. They found no significant differences between respective running speeds at the first VT vs. the first HF threshold, nor between the respective running speeds at the second VT vs. the second HF threshold. A strong correlation was reported between the first VT vs. the first HF threshold, and the second VT vs. the second high-frequency threshold (both $p < 0.001$), respectively. A Bland-Altman plot analysis was used to illustrate that assessment from respiratory sinus arrhythmia gave an accurate estimation of VTs, where high frequency peak of HRV provided a reliable index for detection of VT. This study demonstrated that VTs could be assessed during an incremental running test performed on a track using a RR interval recording HR monitor.

Several studies have investigated vagally modulated HRV parameters over the lifespan of healthy participants (Bonnemeier et al., 2003; Fukusaki, Kawakubo, & Yamamoto, 2000; Umetani, Singer, McCraty, & Atkinson, 1998). One study analyzed the

relationship of age and HRV, derived from short-term recordings, at rest (Fukusaki et al., 2000). Factor analysis was used to eliminate coupling between age and other variables (fitness, triglycerides, total cholesterol, high-density lipoprotein, glucose, systolic blood pressure) and determined that age-related changes in high-frequency modulation at rest, i.e., vagal modulation of HR, was principally influenced by aging per se, and less so by the physiological changes that are associated with aging (Fukusaki et al., 2000). They concluded that when HRV measurements are made at rest, vagally modulated HRV may decline up to age 60.

Tulppo et al. studied beat-to-beat HR dynamics by plotting each RR interval as a function of the previous RR interval (Poincaré plot) during incremental doses of atropine followed by exercise and during exercise without autonomic blockade (Tulppo et al., 1996). The standard deviation of instantaneous beat-to-beat RR interval variability (SD1) and the standard deviation of continuous long-term RR interval variability (SD2) as well as the SD1/SD2 ratio were measured separately and used for vector analysis of the Poincaré plot. Quantitative Poincaré measures were compared with linear measures of HRV at rest and during exercise. Their results showed that all measures of vagal modulation of HR decreased progressively until VT was reached, when sympathetic activation was reflected as changes in the SD1/SD2 ratio. These results show that quantitative two-dimensional vector analysis of a Poincaré plot can provide useful information on vagal modulation of RR interval dynamics during exercise that are not easily detected by linear summary measures of HRV.

Tulppo et al. also analyzed the instantaneous RR interval variability from Poincaré plots at rest and at different phases of a cycle ergometry test in healthy males,

assessing the effects of age and physical fitness on vagal modulation of HR (Tulppo et al., 1998). Poincaré plots were normalized for the average RR interval, which is a measure of vagal activity (Tulppo et al., 1996), then compared them at rest and during exercise among participants of varying ages matched for peak oxygen consumption (VO_2 peak) and among participants with VO_2 peak of 28-37 (poor), 38-45 (average), and 46-60 $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (good) matched for age. An RR interval was interpreted as a premature beat if it deviated from the previous qualified interval by $> 30\%$, where the details of this analysis and the filtering technique are described by Huikuri et al. (Huikuri et al., 1992; Huikuri et al., 1996). RR intervals were higher at rest in the young participants than in the middle-aged or old participants ($p < 0.001$), but the age-related differences in RR intervals were smaller during exercise ($p =$ not significant). The age-matched participants with good, average, and poor VO_2 peak showed no difference in RR intervals at rest ($p =$ not significant), but RR intervals differed significantly among the groups from a low to a moderate exercise intensity level ($p < 0.001$, 100 Watts). The results of their data show that poor physical fitness was associated with an impairment of cardiac vagal function during exercise, whereas aging itself results in more evident impairment of vagal function at rest.

Other studies have shown significant correlations during consecutive measurements in individuals with chronic obstructive pulmonary disorder (Bartels, Jelic, Gonzalez, Kim, & DeMeersman, 2004) as the stability of HRV measurements of parasympathetic activity is of increasing interest in clinical medicine. In one study, reproducibility of parasympathetic activity was determined in 24 hour duration electrocardiograms in normal and ischemic heart disease participants from baseline to

follow-up periods of 2 to 16 weeks, where coefficients of repeatability showed exceptional long-term reproducibility (Nolan et al., 1996). In normal, healthy participants, short term (2 weeks) and long term (7 months) reproducibility of 10 minute electrocardiogram derived time and frequency-domain HRV measurements were observed by Pitzalis et al. where vagal-modulated time-domain measurements showed intraclass correlation coefficients ≥ 0.75 . Similar reproducibility was demonstrated in the frequency-domain measures obtained by way of both Fourier transformations and autoregressive methods (Pitzalis et al., 1996). As a result, time and frequency domain measures provide suitable reproducibility levels in normal and diseased groups in both short-term and long-term studies.

Gender also has an effect on HRV, where in general, women have lower HRV than men. Research has shown these differences are measure dependent (Umetani et al., 1998) where the HRV of male participants is higher than that of age-matched female participants (age 10-29 years). Gender differences have been shown to decrease with age, becoming non-evident around age 50, depending what measurement is used. The work of Stein et al. revealed that in comparisons between older men and women, no statistically significant differences between the groups were found in any of the standard HRV indices (Stein, Kleiger, & Rottman, 1997).

Because measurements of HRV have such promise in the field of exercise physiology, groups with specific diseases and their comorbidities (hypertension, insulin resistance, decreased cardiac output) are often studied. One such study has shown that obese participants have lower HF values than lean participants when measured under 24 hour Holter monitoring (Karason, Molgaard, Wikstrand, & Sjostrom, 1999), while

another study determined that no relationship exists between obesity and vagal control of HR as computed by short-term standardized measures of normalized high-frequency power (Quilliot, Zannad, & Ziegler, 2005). In addition, in a study of obese women vs. lean controls, 24 hour Holter monitoring revealed no difference in high-frequency power, though low-frequency power (a combination of sympathetic and parasympathetic control of HR) was slightly lower in the obese participants (Petretta et al., 1995).

Much literature focuses on the positive association between weight loss, exercise, and vagally modulated HRV. One such study analyzed the changes of autonomic cardiac patterns of severely obese participants in a 3 week weight loss program (Facchini et al., 2003). HRV was determined by an 18 hour Holter monitor once at baseline and again at the end of the final week, where significant changes in vagal modulation of HR were demonstrated in both time- and frequency-domain measurements (which strongly reflect vagal modulation), while an overall weight reduction was also observed via BMI (from 41.4 ± 4.6 to 39.5 ± 4.3 kg/m²). These results indicating a short-term, integrated weight loss program enhanced the autonomic profile of the normotensive, severely obese participants (Facchini et al., 2003). Similarly, Akehi et al. tested a 40 day low calorie diet that resulted in a mean reduction of 18% of body weight (Akehi et al., 2001). During this intervention, Holter monitoring was performed for 24 hours at baseline and again on the final day of the study, displaying significant increases in all vagally modulated HRV indices.

Exercise and weight loss are key elements in the proper maintenance of vagal HRV modulation. A study by Amano et al. describes that 12 weeks of exercise intervention in obese middle aged men and women revealed a significant reduction in

BMI and body fat percentage, and a simultaneous increase in vagal modulation of resting HR (Amano et al., 2001). Poirier et al. analyzed 8 severely obese participants (BMI > 40.0 kg/m²) who participated in a 3 month weight loss program followed by an additional 3 months of a reduced-weight maintenance program. Following the diet regime, a 10% reduction in body weight was established. After the weight loss, the study revealed an increase in high-frequency modulation of HRV, determined by 24 hour Holter monitoring, which showed a significant increase in cardiac vagal modulation (Poirier, Hernandez, Weil, Shepard, & Eckel, 2003). The effects of exercise and reduced calorie intake on HRV were studied in mildly obese, normotensive women (BMI 27.3 ± 0.4 kg/m²). A 3 month program was implemented with the intention of increasing physical activity and modifying eating behavior. The control group was made up of additional women (BMI 27.2 ± 0.6 kg/m²) who did not attend the program. Frequency domain HRV was calculated from 5 minute supine Holter recordings. The intervention group displayed a significant decrease in BMI (25.0 ± 0.5 kg/m²) along with a significant increase in the mean and SD of the RR intervals, low-frequency power, and high-frequency power of HRV. They observed no significant changes in the controls. The changes in these HRV variables (calculated by subtracting baseline values from the follow-up values) had a negative correlation with the change in waist circumference, where Pearson correlation coefficients were between -0.50 and -0.65 ($p < 0.05$). They concluded that the combination of exercise and mild caloric restriction led to changes in HRV that signified improvements in parasympathetic modulation (Ito et al., 2001).

Many studies have shown a significant decrease in HRV among cardiac patients when compared to healthy controls. Bigger et al. points out that this difference has been

less consistent for indices that reflect the vagal control of HR (Bigger et al., 1995); an effect largely due to the increased incidence of sinus arrhythmia (of non-respiratory origin) in the elderly and among cardiac patients (Stein, Domitrovich, Hui, Rautaharju, & Gottdiener, 2005). The improvement of cardiac vagal control after an acute cardiac event (or in patients with congestive heart failure) has been the focus of many studies, utilizing aerobic exercise training as an intervention. When compared to matched sedentary control groups, post-myocardial infarction participants who exercise have shown significant improvements in time and frequency domain measures of HRV (Malfatto et al., 1996; Stahle, Nordlander, & Bergfeld, 1999). Additionally, the sympathovagal balance control of HRV has been demonstrated to go in the direction of an increase in vagal modulation in post- myocardial infarction participants that undergo 8 weeks of an exercise training program (Stahle et al., 1999). De Meersman et al. point out that moderate to intense physical activity, rather than daily expenditure, is the minimal intensity level required to offset the HRV decline in cardiac participants (De Meersman & Stein, 2007). Conversely though, some research suggests that long-term, low intensity physical activity has no effect on autonomic function (Uusitalo, Laitinen, Väisänen, Länsimies, & Rauramaa, 2004).

Although research involving HRV and its clinical role is ongoing, these studies suggest that physical activity and aerobic exercise create a positive effect on the autonomic function of the nervous system (particularly in patients with cardiovascular disease). When analyzed by specific HRV parameters, De Meersman et al. point out that vagal control of HR provides important information regarding the function of the cardiac autonomic nervous system (De Meersman & Stein, 2007), and also advises that HRV

measurements in the elderly must be considered with caution as increases in age are associated with an increased randomness of HR patterns – elevating measurements and possibly misleading the results of vagal modulation. Increased levels of exercise training are associated with improved vagal control of HR, suggesting physical activity may protect against adverse autonomic effects (De Meersman & Stein, 2007). It should be pointed out that there is great potential in using markers of cardiac vagal modulation with intervention studies in particular, with regards to further the understanding of which groups may benefit, and discovering the mechanisms and conditions in which physiological events and thresholds occur.

Physiological Effects of Caffeine

Arousal of the central nervous system and the mobilization of free fatty acids are the general systemic effects of caffeine (one of the methylxanthines). Enhancement of the contractile status of muscles has also been proposed as caffeine has been reported to have an affect on the translocation of calcium inside muscles, promote an increase in cellular levels of cyclic-3',5'-adenosine monophosphate (cyclic AMP), and described to cause a blockade of adenosine receptors in the central nervous system (Powers & Dodd, 1985). Among these cellular mechanisms, it is established that the inhibition of adenosine receptors predominates all others (Dodd, Herb, & Powers, 1993; Keisler & Armsey, 2006; Nehlig & Debry, 1994). Production of plasma catecholamines has been demonstrated to be increased by caffeine (Collomp, Ahmaidi, Audran, Chanal, & Préfaut, 1991; Collomp, Caillaud, Audran, Chanal, & Prefaut, 1990), which may allow the body to adapt to the stress of physical exertion. Nehlig and Debry point out that this production of catecholamines may increase availability of free fatty acids as muscle substrates during

work, thereby allowing glycogen sparing (Nehlig & Debry, 1994). Glycogen sparing may be the result of an increased rate of lipolysis (Costill et al., 1977; Rennie, Winder, & Holloszy, 1976), which may contribute to an increased time to exhaustion during endurance testing.

There is wide agreement that caffeine does not have an ergogenic effect on brief, intense physical activity (Dodd, Brooks, Powers, & Tulley, 1991; Keisler & Armsey, 2006; Perkins & Williams, 1975; Powers, Byrd, Tulley, & Callender, 1983; Tarnopolsky, 1994). Caffeine may however improve on time before exhaustion during prolonged (> 30 minutes) activity of submaximal intensity (approximately 75 to 80% VO_{2max}) (Costill, Dalsky, & Fink, 1978; Kovacs, Stegen, & Brouns, 1998), and therefore may be implicated as an ergogenic aid in submaximal endurance exercise (e.g. marathon running). It is hypothesized the mechanism behind these findings is related to the increased availability of free fatty acids for muscle metabolism which has a glycogen-sparing effect (Costill et al., 1978; Ivy, Costill, Fink, & Lower, 1979; Powers & Dodd, 1985). Nehlig points out that tolerance to the methylxanthine should be taken into account if athletes were to draw any benefit from caffeine absorption prior to a sporting competition (Nehlig & Debry, 1994).

Caffeine's ostensible role as an ergogenic aid (Costill et al., 1978; Graham & Spriet, 1991; Spriet, 1995) has led both athletes and non-athletes to utilize the substance during exercise (Spriet, 1995). It is well documented that caffeine intake effects measurements of blood pressure (Mosqueda-Garcia, Tseng, Biaggioni, Robertson, & Robertson, 1990; Robertson et al., 1978; Sung, Lovallo, Pincomb, & Wilson, 1990; Waring, Goudsmit, Marwick, Webb, & Maxwell, 2003) systemic vascular resistance

(Casiglia et al., 1991; Sung et al., 1990), and HRV (Kolodiichuk & Arushanian, 1991; Nishijima et al., 2002). Studies of caffeine ingestion have found no effect on blood glucose, but have shown increased plasma lactate and free fatty acids levels both at rest and after exercise (Engels & Haymes, 1992).

The autonomic nervous system can be affected by a variety of food (Daly, 1993; Fernstorm & Fernstorm, 1984; Thelle, 1993), many of which are widely consumed throughout the world – specifically those that contain caffeine (tea, coffee, and chocolate). Because of this, the physiological variables such as body surface temperature, peripheral sweat measurements, and blood pressure have been used in the non-invasive detection of changes in the autonomic nervous system – but the effects of food on these variables produce such small changes that they are difficult to measure with reproducibility. From a cardio-interest perspective, analyzing sympathetic and vagal activity involvement in a variable would be of great interest clinically. RR intervals, as measured by HRV, may be useful in this situation where time domain indexes such as SD, CV and MSD have been shown to correlate strongly with vagal tone ($r = 0.87, 0.81$ and 0.92 respectively; $p < 0.001$) (Hayano et al., 1991). Hibino et al. demonstrated caffeine intake enhances autonomic nerve activities, where modulation of the vagal tone was significantly enhanced 20-30 minutes after consumption of caffeine (Hibino et al., 1997).

There are numerous pharmacologic effects caffeine has on influencing the sympathetic nervous system. In caffeine naïve participants, the substance can induce a transient rise in blood pressure (Martin, 1988), high doses may cause tachycardia (Starr et al., 1937), a considerable rise in plasma epinephrine (Izzo, Ghosal, Kwong, Freeman, &

Jaenike, 1983; Smits, Hoffman, Thien, Houben, & van't Laar, 1983; Smits, Thien, & van't Laar, 1985), an increase in plasma rennin activity (Robertson et al., 1978), increased plasma lactate and free fatty acids levels both at rest and after exercise (Engels & Haymes, 1992), and at high doses, has been shown to induce ventricular arrhythmias in canine and rabbit hearts in vivo (Ihida et al., 1996; Mehta, Jain, Mehta, & Billie, 1997). Caffeine also influences thermogenic and lipolytic effects (Acheson, Zahorska-Markiewica, Pittet, Anantharaman, & Jequier, 1980).

In a study on the influence of caffeine, Flinn et al. utilized a 3 minute stage cycle ergometry test, and revealed that in caffeine trials, participants worked significantly longer and performed more work ($p < 0.05$) than they did in either control or placebo trials (Flinn, Gregory, McNaughton, Tristram, & Davies, 1990). A large ($10 \text{ mg}\cdot\text{kg}^{-1}$) dose of caffeine taken 3-4 hours prior to exercise was tested, where no significant changes in between trial HR were observed.

Dodd et al. looked at the effects of caffeine on graded exercise performance in caffeine naïve (caffeine consumption $< 25 \text{ mg}\cdot\text{day}^{-1}$) and caffeine habituated (caffeine consumption $> 300 \text{ mg}\cdot\text{day}^{-1}$) participants (Dodd et al., 1991). Three cycle ergometer trials (placebo, $3 \text{ mg}\cdot\text{kg}^{-1}$ dose, and $5 \text{ mg}\cdot\text{kg}^{-1}$ dose) separated by 7 days took place. The caffeine naïve group in that study showed significant increases in resting HR and expired ventilation volume after the $3 \text{ mg}\cdot\text{kg}^{-1}$ and $5 \text{ mg}\cdot\text{kg}^{-1}$ doses as well as a significant increase in resting VO_2 after the $5 \text{ mg}\cdot\text{kg}^{-1}$ dose. Their results revealed no significant differences for exercise expired ventilation, VO_2 , respiratory exchange ratio, or time to exhaustion. Dodd et al. reported no significant differences ($p < 0.05$) in LT or VT between treatments in either group. The caffeine habituated participants showed a

significant increase ($p < 0.05$) in resting plasma free fatty acids concentration only during the $3 \text{ mg}\cdot\text{kg}^{-1}$ and $5 \text{ mg}\cdot\text{kg}^{-1}$ dose treatments.

Similarly, a constant load cycle ergometer exercise test (approximately 80% of VT) was utilized as Powers et al. conducted two trials of a single blind experimental procedure (placebo and $7 \text{ mg}\cdot\text{kg}^{-1}$ body weight of caffeine) where results revealed no significant difference ($p > 0.05$) in the mean response time for VT between treatments (Powers, Dodd, Woodyard, & Mangum, 1986).

Powers et al. also used graded cycle ergometry to assess the effects of caffeine on metabolism and performance, where ingestion of $5 \text{ mg}\cdot\text{kg}^{-1}$ body weight of caffeine revealed no significant difference ($p > 0.05$) in time to exhaustion between the two experimental treatments (Powers et al., 1983). That study also showed that ingestion of caffeine brought about significant ($p < 0.05$) increases in plasma levels of both free fatty acids and glycerol compared to values obtained during the placebo treatment, and that the rate of BLa acid accumulation was not significantly different ($p > 0.05$) between the two trials. These data suggest a small dose of caffeine does not change the rate of BLa accumulation nor does it enhance performance during graded cycle ergometer exercise.

Established studies have demonstrated that caffeine ingestion improves performance during prolonged exercise to exhaustion (Costill et al., 1978; Kovacs et al., 1998), a result of an upregulation of circulating free fatty acids (Graham & Spriet, 1991). Kovacs et al. studied the effect of different dosages of caffeine on metabolism, caffeine excretion, and performance (Kovacs et al., 1998). With blinded ingestion of caffeine, their participants demonstrated improved performance of a 1 hour time trial with caffeine supplementation. The post-exercise urinary caffeine concentration (range 1.3-2.5

microg/ml) was dose dependent and always far below the doping level of the International Olympic Committee (12 microg/ml) in all of their participants. The caffeinated carbohydrate-electrolyte solution in which their participants drank did not enhance free fatty acid availability, ruling out the fact that performance improvement resulted from enhanced fat oxidation. Their study concluded that the addition of relatively low amounts of caffeine to carbohydrate-electrolyte solution improved performance.

The observation of endogenous catecholamine release (Bangsbo, Jacobsen, Nordberg, Christensen, & Graham, 1992; Kalmar & Cafarelli, 1999; Van-Soeren & Graham, 1998) has revealed that caffeine ingestion may enhance activity of the sympathetic nervous system during rest as well as exercise. Whether or not this increase in sympathetic activity has a significant effect on measurements of HRV will be a clinically relevant issue, and deserves to be addressed.

General Health

The study of factors that affect the health and illness of people is known as epidemiology ("Dorland's Medical Dictionary," 1980), which serves as the cornerstone of knowledge and judgment in the realm of public health and preventive medicine. From the Greek derivation, *epi* meaning "upon" and *demos* meaning "people" comes the word epidemic, a disease that affects many people at the same time in the same geographical area ("Taber's Cyclopedic Medical Dictionary," 1997) often at a rate that surpasses what may be "anticipated" based on recent experience. Data to support the debate regarding an epidemic emergence of modern chronic diseases have consistently been emerging,

especially in the latter part of the 20th century (Booth et al., 2000), a time period which has demonstrated a remarkable increase in chronic diseases.

Chronic Diseases

America's populace is shifting to that of an older generation. Over 3.5 million United States citizens are 85 years or older, and there will be forthcoming a considerable increase in the relative size of the elderly group after the year 2011, when the oldest members of the baby-boomers (those born in 1946) reach 65 years of age. By the year 2040, the Census Bureau anticipates there will be at least 8-13 million Americans aged 85 or older (Campion, 1994). These numbers imply that, in addition to their increasing incidence in our younger generation, most chronic diseases are also regarded as age-related diseases, since they clinically manifest themselves to a greater degree later in life (Must et al., 1999). Generally, years after the initial causes of a particular disease takes place; these continual problems begin to surface. Termed chronic diseases, they are slow in progress and long in continuance ("Dorland's Illustrated Medical Dictionary," 1974). The upcoming years may therefore exhibit drastic increases of chronic diseases unless there is an implementation for better preventive measures against its progression (Booth et al., 2000). Proper diet and regular physical activity have long been considered the cornerstone of preventive medicine. There is a dire need to establish easier and more cost-effective ways to implement group specific (healthy, cancer, cardiovascular disease, geriatric, and obese) exercise prescriptions into society before the general state of chronic illness becomes worse.

Booth et al. reports the realm of biomedical science has increased the understanding of mechanisms underlying the treatment of chronic disease, however

contends that most biomedical advances for chronic diseases have made their greatest impact *after* the disease is clinically observed and diagnosed (Booth et al., 2000). Advances in the field of biomedical research are of great importance to the large number who suffer from chronic disease and should not be underestimated. However, many in medically related fields often consider preventive medicine a lesser area of research. Unfortunately, this thought process results in a disorder of the health care system – treating the symptoms first, rather than the cause of a disease. Among others, Booth stresses that current research efforts against chronic disease are incomplete, due to the tendency to focus so strongly on the secondary and tertiary prevention of disease (i.e.: treatment of disease after it has manifested), instead of primary prevention (Booth et al., 2000). The current crisis the U.S. faces with overweight and obesity are examples of health related issues that may someday be considered chronic, and are quickly spiraling out of control. Reports of increasing prevalence of overweight and obesity have become commonplace, and the incidence of obesity appears to be increasing, where poor diet and physical inactivity may soon overtake tobacco as the leading cause of death (Mokdad, Marks, Stroup, & Gerberding, 2004). Kassirer et al. (1998) contend that:

“A progressive fattening of the population is not inevitable. We need to do a better job of educating people about healthful diets, including the calorie content of common foods, without promoting fetishes. Encouraging lifelong, regular exercise in children may well have the greatest effect in terms of preventing obesity, as well as numerous other benefits. If the time children now spend in front of the television eating junk food and watching advertisements for more junk food was instead spent in physical activity, leanness would be virtually ensured. Healthful eating habits and regular exercise become even more critical in young adulthood, when a tendency toward obesity typically appears” (p. 54) (Kassirer & Angell, 1998).

The issue of obesity is but one of many persistent problems we will face in upcoming years, and a key element in fighting against these diseases is to expand biomedical research into the (underdeveloped) field of primary prevention (Booth et al., 2000). Maintaining and caring for the physical self prior to preliminary problems and eventually chronic disease take effect, is a concept that is easily understood but difficult to implement. Healthy living includes essential care for the physical entity, a practice that can have positive long-term effects if regular doses of exercise and a well-balanced, nutritious diet form its foundation. It represents an alternative to the mainstream trend that has the ability to ease suffering before diseases become chronic, and is far more cost effective in terms of health care prices. Preventive medicine is the basis of overall wellbeing.

The fundamental causes of most modern chronic diseases are considered by some researchers as heterogeneous and highly dependent on the environment; as is seen in coronary heart disease, which affects just a small proportion of individuals solely on the basis of a single gene defect. Instead most coronary heart disease patients suffer from a combination of environmental factors that overlap into a multitude of conditions such as atherosclerosis, hypertension, type 2 diabetes, hyperinsulinemia, obesity, and elevated triglycerides – sometimes referred to as the “metabolic syndrome” (Booth et al., 2000). In much the same way, the increased incidence of type 2 diabetes and obesity is not due to new gene mutation, rather the existing genes that code for a diabetic predisposition are given greater opportunity to capitalize because of the excessive ways in which our Western diet and lifestyle exist. The American Heart Association points out that the large increase in heart disease deaths from 1900 to 1996 (American Heart Association, 1998) is

not due to changes in the human genome, but our lack of regular physical activity and exercise. Eaton and Konner (1985) noted, “The human genetic constitution has changed relatively little since the appearance of truly modern human beings, *Homo sapiens sapiens*, about 40,000 years ago” (p. 284) and continue that, “chronic illnesses affecting older, post reproductive persons could have had little selective influence during evolution, yet such conditions are now the paramount cause of morbidity and mortality in Western nations” (p.285) (Eaton & Konner, 1985). The relatively recent shift from physically active lifestyles to one inundated with an increase in technology, computers, television, sedentary lifestyles, and static workdays may in large part account for the higher prevalence of many diseases seen today.

Chronic Diseases: Obesity

The past three decades have revealed a drastic increase in the prevalence of obesity, which has now become a public health dilemma in the U.S. (Ogden et al., 2006; US Surgeon General, 2001). Childhood obesity has reached epidemic proportions where 17% of US children are overweight, and its incidence has risen dramatically in the last several years (Ogden et al., 2006). Prevalence rates are even higher for minority children such as Hispanic and African Americans (Kimbrow, Brooks-Gunn, & McLanahan, 2007; Wang & Zhang, 2006). Childhood overweight has also been shown to predict adult overweight (Janssen et al., 2005) where comorbidities such as cardiovascular disease, type 2 diabetes, hypertension, dyslipidemia, and metabolic syndrome may carryover into adulthood.

A critical problem with obesity is its carryover to multiple comorbidities including insulin resistance and breast cancer prognosis. This is of immense concern to

the African American breast cancer survivor group (Chlebowski, Aiello, & McTiernan, 2002). It is known that proportionally, a greater number of African Americans, as compared to European Americans, have high insulin levels, are diabetic, and are obese (Davidson, 2001; Mokdad et al., 1999; Okosun, 2001). For the most part, weight loss has not been easy to attain in African-Americans, and the maintenance of weight loss has been equally difficult to demonstrate in nearly any group (Kumanyika, 2001).

Obesity is estimated to account for nearly 112,000 deaths annually in the U.S. (Flegal, Graubard, Williamson, & Gail, 2005), and the current trend is on an upward rise. Because the obesity problem has reached such epic levels, the use of a convenient measure to determine body mass index has been established and for practical purposes, the BMI is defined as $(\text{weight (kg)}/\text{height (m)}^2)$ and is widely used to assess obesity among children and adults (Guillaume, 1999; Kuczmarski et al., 2000; World Health Organization, 2000). Obesity is rapidly approaching tobacco as the leading cause of preventable morbidity and mortality (Mokdad et al., 2004), and some contend the obesity epidemic in the U.S. is not unlike the type 2 diabetes epidemic in the sense that its increasing trend is not simply a function of a group shift from middle to older ages, rather a real phenomenon (Booth et al., 2000).

Obesity is considered a comorbidity of some of the most ubiquitous diseases of the present day (Jung, 1997; Must et al., 1999) and it is known that the number of comorbidities exhibited in an individual grows with increasing body weight. Must et al. reported that a higher incidence of diseases such as hypertension, osteoarthritis, and gallbladder disease are related to increasing obesity (Must et al., 1999), while Lewis et al. adds that multiple comorbidities arise from the primary disease obesity, including heart

disease, atherosclerosis, increases in cholesterol, certain types of cancer, diabetes, stroke, muscle and bone disorders (Lewis & Man, 2007). Obesity may be caused by the excessive availability of unhealthy foods, increased consumption and changing trends in eating habits, the availability of high-calorie beverages, and severe lack of physical activity (Lewis & Man, 2007). Jung et al. also points out that a BMI ≥ 35 kg/m² is associated with a 42-fold increase in the risk of type 2 diabetes in men and a 93-fold increase in women; and additionally, a 20% rise in body weight in men increases the risk of coronary heart disease by 86% (Jung, 1997). If preventive measures such as diet regulation and proper exercise prescription were implemented early in childhood and continued throughout life, the prevalence of diseases such as type 2 diabetes and obesity would be greatly diminished. Tremendous advances to these problems could be made if an easy, inexpensive, and non-invasive approach to measuring the same physiologically based thresholds as researchers study in a laboratory were made available to the general public for widespread use.

The U.S. is not alone in the epidemic of obesity, as its incidence is a problem that has dramatically increased worldwide in recent years (Visscher & Seidell, 2001). Among Iranian schoolgirls, where the prevalence of overweight and obesity in this sample was high, physical activity was shown to be significantly different between obese and non-obese children (Mozaffari & Nabaei, 2007). A causal relationship between obesity and asthma has even been suggested by researchers in Chile, where a complex relationship involving the interaction of genetic and environmental factors, as well as biological mechanisms (immunologic, inflammatory, hormonal, nutritional, mechanical, and others related to physical activity) contribute at once in triggering both diseases (Castro-

Rodriguez, 2007). In Hungary, a study mapping policy options regarding trends in the prevalence of overweight and obesity revealed broad support for changes in current patterns of food consumption and levels of physical activity (Horvath, Pankotai, & Szabolcs, 2007). It has been argued in Australia, that obesity should not merely be viewed by the government as a public health issue, but additionally, an obstacle to productivity and depletion on economic resources (Kouris-Blazos & Wahlqvist, 2007). The Australian government has even made changes to their healthcare system so patients with chronic illnesses due to obesity can be referred to an exercise physiologist and dietitian and receive a Medicare rebate, in an effort to cut away at their obesity levels (Kouris-Blazos & Wahlqvist, 2007). The impact of this disease on a region's economy can cost thousands of jobs and reach into the billions of dollars (Frezza, Wachtel, & Ewing, 2006) and when the efforts of physical activity and conventional treatments for obesity are ineffective, bariatric surgery quickly becomes an alternative method in the war against obesity. In an effort to establish a cost-effective model surrounding the obesity epidemic, European researchers concluded that participants with type 2 diabetes and a BMI ≥ 35 kg/m² found that adjustable gastric banding and gastric bypass were effective at 5-year follow-up in cost-saving in Germany and France, and the U.K. (Ackroyd, Mouiel, Chevallier, & Daoud, 2006).

Obesity crosses borders and affects many groups. For individuals who suffer from multiple diseases (cardiovascular disease, cancer, hypertension), obesity serves as a gateway to further complicate their comorbidities. Breast cancer is the most frequently diagnosed cancer among U.S. women (US Cancer Statistics Working Group, 2005). Regarding its treatment, the issue of obesity is of immense concern given that recurrence

rates and survival in early-stage disease are both negatively impacted by obesity (Chlebowski et al., 2002; Goodwin et al., 2002). The effect of obesity on breast cancer recurrence has been evident in both pre- and post-menopausal women, a result not observed in the effect of obesity on *de novo* breast cancer risk. Case in point: in a study of young women, higher body mass was associated with tumors of higher cellular proliferation and decreased survival from breast cancer (Daling et al., 2001).

Some studies in premenopausal women argue that the risk of breast cancer is actually lowered in overweight to obese participants, which is possibly explained by an increased frequency of anovular menstrual cycles (Freidenreich, 2001). This in turn may result in less exposure to estrogens wherein one report describes a subsequent reduced breast cancer risk (Campbell & McTiernan, 2007), but points out that this should not overshadow the fact that overweight and obesity also result in lower progesterone levels, which may play a key role in the increased endometrial cancer risk for this group because of unopposed estrogens (Key, Allen, Verkasalo, & Banks, 2001).

Overweight or obese postmenopausal women display an increased risk of postmenopausal breast cancer principally due to larger amounts of adipose tissue where estrogen is produced (Morimoto et al., 2002). There are unique biological factors in obese breast cancer survivors that are not typically present in obese persons who have never had a cancer diagnosis. An increase in stress and depression is often the result of a diagnosis of cancer, which can negatively affect weight loss attempts (Brady et al., 1997; De Florio & Massie, 1995). Additionally, sarcoplasmic weight gain is often the result of chemotherapy for breast cancer (Demark-Wahnefreid et al., 2001; Demark-Wahnefreid, Rimer, & Winer, 1997), where the commonly used drug tamoxifen has been shown to

decrease cholesterol levels and increase triglycerides (Joensuu, Holli, Oksanen, & Valavaara, 2000). Data also indicates that breast cancer patients may exhibit disturbances in lipid metabolism, presenting higher levels of plasma triglycerides than non-cancer controls (Goodwin et al., 1997; Hoyer & Engholm, 1992; Schreier et al., 1999). Insulin levels in breast cancer patients have been shown to be higher than in normal healthy controls (Stoll, 1999), and breast cancer patients and diabetics have demonstrated relatively increased levels of oxidative stress (Djuric et al., 2001; Frenkel et al., 1998; Ruhe & McDonald, 2001; Saintot et al., 2002; Tagesson, Kallberg, Klintonberg, & Starkhammar, 1995). For these reasons, weight-loss attempts in breast cancer survivors may therefore have different effects than those studied in other obese groups.

Obesity may also have an exacerbating effect on initial disease prognosis and treatment (Chlebowski et al., 2002; Demark-Wahnefreid et al., 2001; Demark-Wahnefreid et al., 1997; Schapira et al., 1994), as additional weight gain brings about a negative impact on quality of life (McInnes & Knobf, 2001). Some reviews indicate that in studies on prognosis and weight gain after breast cancer diagnosis, participants who gained relatively more weight during treatment demonstrated a lower chance of survival (Bonomi, Bunting, & Fishman, 1984; Camoriano et al., 1990; Chlebowski et al., 2002; Chlebowski et al., 1986). Insulin resistance can be improved by weight loss of as little as 5-10% of initial body weight (Chlebowski et al., 2002; Hu et al., 2001; Knowler et al., 2002; Tuomilehto et al., 2001), and as a result, its effect on obesity may play a role in breast cancer prognosis. As previously mentioned, proportionally, a greater number of African Americans, as compared to European Americans, have high insulin levels, are diabetic, and are obese (Davidson, 2001; Mokdad et al., 1999; Okosun, 2001) and the

NHANES data set from 1994-98 details that 52.3% of African American women were reported as overweight, while 37.6% of the same group were obese (National Center for Health Statistics, 2001). Post-diagnosis breast cancer, African American women have been reported to gain twice as much body weight as their European American counterparts (Rock et al., 1999). With a proper exercise prescription tailored to the obese African American female breast cancer survivor group, a change in the risk of recurrence may take place. Because of the difficulties associated with metabolic testing, an easy to use HR based model (derived from HRV and sympathetic nervous system measurements) would be helpful in locating established thresholds, that can be applied to tailored exercise prescriptions for this group.

Chronic Diseases: Cardiovascular Disease

Heart disease and stroke, the two principal components of cardiovascular disease, rank first and third, respectively, among the leading causes of death in the U.S. (National Center for Health Statistics, 2005). Cardiovascular disease is the leading cause of death worldwide and also a principal cause of disability (Lopez et al., 2006; Murray & Lopez, 1996). Coronary heart disease was responsible for the greater part of deaths in the U.S. in the 20th century (American Heart Association, 1998) and since 1900, cardiovascular disease has been the number one killer in the U.S. every year but one (1918). Cardiovascular disease is the cause of more deaths each year than the next seven prevalent causes of death combined (American Heart Association, 1998). According to the American Heart Association, the number of deaths related to diseases of the heart has risen by 37% from 1950 to 1996 (American Heart Association, 1998).

Approximately one in three U.S. adults (~71.3 million) have one or more types of cardiovascular disease (Thom, Haase, Rosamond, Howard, & Rumsfeld, 2006), where the most common conditions include hypertension (65 million), coronary heart disease (13.2 million), stroke (5.5 million), heart failure (5 million), and congenital heart defects (1 million) (Thom et al., 2006). In the U.S., cardiovascular disease accounted for 34.4% of the 2.4 million deaths in 2003 (Hoyert, Heron, Murphy, & Kung, 2006) and remains a major cause of health disparities and the rising cost of health care. A 2006 study on health care expenses and lost productivity due to cardiovascular disease reported an excess of \$400 billion (Thom et al., 2006). The lack of physical activity and regular exercise has no doubt contributed to the problem the U.S. faces with regard to obesity, cardiovascular disease, and the comorbidities that follow.

Some researchers believe that despite the vast cardio-protective role physical activity has to offer, pediatricians should put into operation even more intensely preventive strategies based on physical activity, diet, and behavior in an effort to avert type 2 diabetes and cardiovascular disease at an early age (Balagopal, 2006) as strategies to prevent obesity and its complications are imperative. Given the anticipated increase in the older adult population of the U.S., the current obesity epidemic, a gross under use of prevention strategies, and immoderation of risk factors, the cardiovascular disease burden will only distend in the future (Mensah & Brown, 2007). As age is considered a major risk factor to cardiovascular morbidities and mortalities, cardiovascular disease is an epidemic that is projected to worsen as the U.S. population above the age of 65 continues to increase. Additionally, the ever-increasing presence of a lack of exercise greatly contributes to the cardiovascular disease crisis in the U.S. De Meersman et al. contends

that ultimately, cardiovascular diseases have one common denominator – perturbed autonomic balance – which displays either a decrease in vagal modulation, an increase in sympathetic modulation, or a combination of both (De Meersman & Stein, 2007). Regardless of the commonalities or origin, the outcomes of cardiovascular disease may be altered by regular exercise. Research in the field of exercise physiology requires further development in studying the autonomic nervous system pathways for a greater understanding of this suggestion. An increased adherence to clinical guidelines and a continual stress on lifestyle changes will be crucial for the effective prevention and control of the disease (Mensah & Brown, 2007).

General Considerations of Breast Cancer Formations

One in eight U.S. women may develop breast cancer according to reports by the American Cancer Society (Jemal et al., 2003). Breast cancer has a number of recognized risk factors including: family history, menarche before age 11, menopause after age 54, nulliparity (never having borne children), late age at first pregnancy, increased consumption of alcohol, and obesity (among post-menopausal women) (McPherson, Steel, & Dixon, 2000). Primary prevention of breast cancer is of paramount importance as the risk of death can be reduced by approximately 25% with periodic mammography, but despite the substantial reduction in risk that interventions can offer, the actual practice of screening and recommending treatment to high risk women is rare (Cummings, 2007). Many studies recommend that regular exercise, a reduction of body weight and a decrease or cessation in alcohol consumption may reduce the risk of breast cancer (Eliassen, Colditz, Rosner, Willett, & Hankinson, 2006; McTiernan et al., 2003; Smith-Warner et al., 1998). One study linked a low fat diet to a 9% reduction in risk of breast

cancer, though the results was not statistically significant (Prentice, Caan, & Chlebowski, 2006); conversely however, many large prospective studies have found no association between fruits and vegetables consumption and risk of breast cancer (Malin et al., 2003; Smith-Warner, Spiegelman, & Yaun, 2001). Other lifestyle changes such as increasing dietary folate may reduce the increased risk of breast cancer due to alcohol intake (Baglietto, English, Gertig, Hopper, & Giles, 2005; Tjønneland et al., 2006). Some researchers believe, however, that these interventions can reduce the risk of breast cancer by 5–10% (Cummings, 2007).

Although following a healthy lifestyle is an excellent means of primary preventive intervention, women at high risk for breast cancer may be advised to reduce their risk further by pharmacologic means. Chemoprevention in the form of selective estrogen receptor modulators, such as tamoxifen and raloxifene, have potential adverse effects but large clinical trials have shown a reduced risk of invasive breast cancer by about 50% by reducing the incidence of estrogen receptor positive (but not estrogen receptor negative) cancer (Barrett-Connor et al., 2006; Cummings et al., 1999; Fisher et al., 1999).

Women with elevated levels of estrogen and androgens have a higher occurrence of developing breast cancer (Key, Appleby, Barnes, & Reeves, 2002), but physical activity is often cited as a potential mechanism for decreased risk in breast cancer when its effects are considered upon: age at menarche, menstrual cycle function, and level of endogenous sex steroid hormone levels in girls and young women (Bernstein, Henderston, Hanisch, Sullivan-Halley, & Ross, 1994). Among its numerous benefits, regular exercise has the ability to reduce oxidative stress and control specific hormone

levels and serum concentrations – thereby having the potential to reduce the risk associated with breast cancer. Research has also shown that beyond the energy cost it requires, exercise and other stressors do not induce disruptive effects on reproductive function in women (Loucks, 2003; Loucks & Redman, 2004; Williams, Helmreich, Parfitt, Caston-Balderrama, & Cameron, 2001). Some studies (Cauley, Gutai, Kuller, LeDonne, & Powell, 1989; McTiernan et al., 2006) have shown that increases in physical activity in postmenopausal women are associated with lower serum concentrations of estradiol, estrone, and androgens after adjustments for BMI, however some studies contradict these findings (Verkasalo, Thomas, Appleby, Davey, & Key, 2001). Positive effects of physical activity have a close relationship to body composition as the primary source of estrogen in postmenopausal women is from aromatization of androgen precursors in peripheral adipose tissue (Key et al., 2001). Women with low physical activity (≤ 6.5 MET-hours per week) and high BMI (≥ 29.0) have shown higher levels of estrone, estradiol, and free estradiol as well as low levels of sex hormone binding globulin (Howard et al., 2006) when compared to women of comparable BMI who were active or women of low BMI who reported either low or high physical activity (McTiernan et al., 2006).

Obese, postmenopausal women have serum concentrations of estradiol up to two times greater than postmenopausal women who are lean (Key et al., 2001). In women, a higher BMI is linked to a decrease in SHBG which leads to prominent increases in free estradiol levels (Key et al., 2001). Estrogens are essentially metabolized through two mutually exclusive pathways to produce either 16α -hydroxyesterone (16α -OHE1) which acts like estrogen, and 2-hydroxyesterone (2-OHE1), which has a minimal to no

estrogenic effect (Campbell & McTiernan, 2007). Changes in the metabolism of estrogens may be connected to certain types of cancer developments, breast cancer in particular (Campbell & McTiernan, 2007). Researchers have reported that with an increase in physical activity, a greater ratio of 2-OHE1 to 16 α -OHE1 is revealed in women. When control participants were compared to female athletes, the athletes demonstrated a higher ratio of 2-OHE1 to 16 α -OHE1 (Russell, Mitchell, Musey, & Collins, 1984), as was also the case in women with higher aerobic capacities (measured by VO_{2max}) (Campbell, Westerlind, Harber, Friedenreich, & Courneya, 2005), as well as with women who self-reported daily physical activity (Bentz, Schneider, & Westerlind, 2005; Matthews et al., 2004). In addition, it has been shown that high-intensity training also increased the 2-OHE1 to 16 α -OHE1 ratio, which may result in menstrual abnormalities (Russell et al., 1984; Russell, 1984; Snow, Barbiebi, & Frisch, 1989).

Defects in insulin action and decreases in rates of glucose disposal are causes of insulin resistance, which can be characterized by hyperinsulinemia (increased levels of insulin in the blood), hyperglycemia (elevated levels of fasting blood glucose), hypertension (increased levels of blood pressure), and dyslipidemia (elevation of plasma cholesterol and/or triglycerides of a low high density lipoprotein level that contributes to atherosclerosis) and affects approximately 22% of U.S. adults (Ford, Giles, & Dietz, 2002). Insulin resistance has been associated with an increased risk of breast, colon, endometrium, pancreas, and stomach cancers (Frank, 2006; Kaaks & Lukanova, 2001). This increased prevalence of cancer (Hu et al., 1999; Saydah et al., 2003) and mortality (Saydah, 2003) has also been revealed in groups with type 2 diabetes and/or impaired glucose tolerance. Tumor growth can be exacerbated by insulin via a number of

pathways: stimulation of cell proliferation, inhibition of apoptosis, regulation of the synthesis and bioavailability of sex steroid hormones, and/or inhibition of sex hormone binding globulin synthesis (Kaaks & Lukanova, 2001).

Importance of Exercise: Preventive Medicine

Primary prevention is a key factor in many diseases (Booth et al., 2000), and physical inactivity is a large contributor to the problems that manifest. An editorial by members of the Centers for Disease Control and Prevention, Koplan and Dietz, (Koplan & Dietz, 1999) states the comprehensive way in which physical inactivity has established itself in our environment,

“despite the pervasive conceptual preference for being lean and active, the environments and behaviors that have been developed make both characteristics difficult to achieve. Far too many people appear to have accepted the determinants of the problems of overweight and inactivity, and rely on ‘treatments’ in the forms of myriad ineffective diet remedies and nostrums. As with many health issues, it is essential to emphasize prevention as the only effective and cost-effective approach” (p. 1581).

In a large study (n = 26,942) analyzing the impact of body fat percentage on prevalence of and mortality from cardiovascular disease, Calling et al. reported that body fat percentage was significantly related to incidence of coronary events, ischemic stroke, and cardiovascular disease mortality in women (Calling, Hedblad, Engstrom, Berglund, & Janzon, 2006). This study also suggested physical activity has the ability to reduce the raised cardiovascular risk associated with high body fat percentage.

The current generation of U.S. adults may not fully understand the repercussions their lifestyles will eventually have on them. With a severe lack of proper diet or adequate exercise, today’s youth follows the dangerous example set forth by their elders. Hazardous lifestyle trends may lead women, in particular, to higher risks of cancer by

mechanisms which include increased estrogens and testosterone which, in turn lead to a higher incidence of breast and endometrial cancers; hyperinsulinemia and insulin resistance leading to increased risks of colon, breast, and pancreatic cancers; and increased inflammation and depressed immune function leading to other types of cancer (McTiernan, Ulrich, Slate, & Potter, 1998). Campbell et al. notes that an understanding of the mechanisms by which unhealthy lifestyle trends influence cancer risk will provide confirmation regarding optimal exercise prescription for cancer risk reduction (Campbell & McTiernan, 2007), but warns that the relationship that overweight, obesity, sedentary lifestyles and cancer share is a complicated one.

Additionally, dietary factors are continually analyzed for their roles in cancer prevention. The importance of fruit, vegetables, and whole grain consumption has been proven in two recent meta-analyses (Key et al., 2004; Williams & Hord, 2005). Changes in dietary intake can alter fatty acid levels in breast tissue and nipple aspirates within 1-3 months (Bagga et al., 1994; Bagga et al., 1997), and a low-fat diet has revealed beneficial effects on mammographic patterns as well as systemic oxidative stress (Djuric et al., 1991; Ensley et al., 1994; Fürst, Auer, Nordevang, Nilsson, & Holm, 1993; Nordevang, Azavedo, Svane, Nilsson, & Holm, 1993). Dietary fat intake is considered a risk factor in cancer prevention; however a recent randomized controlled dietary cancer prevention intervention study reported only a relatively small (9%), statistically non-significant decrease in invasive breast cancer (Prentice, 2006).

Importance of Exercise: Health

Thousands of years after the appearance of the modern human being (i.e., *Homo sapiens sapiens*), a large part of the U.S. population currently finds the demand for a

physically active lifestyle almost nonexistent. According to Eaton et al., ours is an inherited genome that evolved within a physically active lifestyle which predominated the majority of human existence, and with the beginning of the industrial revolution, a little more than 100 years ago, the hunter-gatherer societies of our ancestors seem quite distant (Eaton & Konner, 1985). The industrialization of our society plays a key role in the regression of physical activity, where in many cases; those who acquire any exercise at all must deliberately plan it into their day. This greatly contrasts with the few remaining hunter-gatherer societies of today, where a physically demanding lifestyle still dominates. Metabolic measurements of Peruvian natives are nearly double that of U.S. men in average energy expenditure (Montgomery, 1978). Eaton and Konner maintain that diseases such as coronary heart disease, hypertension, diabetes, and some forms of cancer are nearly unheard of in present-day hunter-gatherer societies, even in persons over 60 years of age (Eaton & Konner, 1985). Researchers believe this higher incidence of disease in technologically developed nations is in part due to the physical inactivity that is the basis of our lives (Booth et al., 2000). The U.S. Centers for Disease Control and Prevention has stated the proportion of the total population reporting physical activity more than five times per week was approximately 23%. Additionally, there was a reported drop from 42% to 27% of high school students who took part in daily physical education (Centers for Disease Control and Prevention, 1999).

Amplified systemic oxidative stress levels are associated with increased risk of various cancers, including that of the breast (Boyd & McGuire, 1990; Brooks et al., 1998; Frenkel et al., 1998). Diet modification is an effective way to reduce both oxidative stress and cancer risk in animals, and it has been shown to have antioxidant effects in

lymphocytes of obese persons as well (Dandona et al., 2001; Hart et al., 1999). Additionally, physical activity has been linked with an increased antioxidant capacity in blood (Covas et al., 2002; Lesgards et al., 2002). Booth et al. states that physical inactivity and inappropriate diet are two unhealthy behaviors that combined, account for an estimated 28% of all preventable deaths in the U.S. annually (Booth et al., 2000). The benefits of physical activity and exercise are widely accepted today, however, the U.S. continues to avert preventive measures that are simple and beneficial. Booth et al. (2000)

notes:

“The number of chronic diseases and associated financial costs potentially produced by physical inactivity is still much larger than generally appreciated. Indeed, with the possible exception of diet modification, we know of no single intervention with greater promise than physical exercise to reduce the risk of virtually all chronic diseases simultaneously” (p. 778). (Booth et al., 2000)

This standpoint regarding the importance of exercise for overall health and wellbeing is shared among public health and human biology researchers. Many however, still do not assign to this concept the proper level of importance it actually deserves.

Grundy (1999) explains:

“Certainly, obesity and physical inactivity are the dominant causes of insulin resistance, although genetic factors undoubtedly affect its severity. The most effective therapies for insulin resistance are weight loss and increased physical activity. Efforts to achieve a desirable body weight and to enhance physical activity are essential components of primary prevention, in both public health and clinical arenas” (p. 993). (Grundy, 1999)

Herrero et al. reveals possible relationships between cardiorespiratory fitness and well-being in breast cancer survivors, where data emphasizes the need for this group to engage in programmed cardiorespiratory exercise training, mainly designed to improve VT (Herrero et al., 2006). Despite solid evidence surrounding the relation of women who

are physically active throughout their lifetime and the reduced risk for breast cancer (Friedenreich, 2001), epidemiologic studies on this association have revealed contradictory conclusions (Gammon, John, & Britton, 1998). A possible explanation for the inconsistencies reported may be the assessment of physical activity at different time periods in a woman's life (Friedenreich & Orenstein, 2002) where Kruk points out that household chores and walking may be activities that are an important component of physical activity among post-menopausal women (Kruk, 2007).

The body of science relating obesity to a number of comorbidities (e.g., type 2 diabetes, cardiovascular disease, and stroke) has been well documented. Currently, the association obesity has with cancer is becoming increasingly more established. Avoidance of weight gain for cancers of the breast (postmenopausal), colon, endometrium, esophagus, and kidney have been reported by the International Agency for Research on Cancer Working Group (International Agency for Research on Cancer, 2002), while links of body composition and weight have been related to cervix, gallbladder, liver, ovary, pancreas, prostate, and certain hematopoietic cancers (Calle & Thun, 2004). It has been reported that a higher BMI leads to a decreased risk of premenopausal breast cancer, however, being overweight or obese increases the risk of postmenopausal breast cancer (van den Brandt et al., 2000). Consequently, a higher percentage of body fat, increased waist-hip ratio, and adult weight gain are associated with an increased risk in postmenopausal breast cancer (Patel & Bernstein, 2006).

The risk of breast cancer tends to be reduced with lifetime occupational physical activity, but the dose-response trend is not always significant among women (Kruk, 2007). There is an ever increasing amount of literature on the risk of breast cancer and its

relation to occupational physical activity, where the overwhelming majority of studies (for review see; (Kruk, 2005)) maintain that this type of physical exertion has a protective effect on risk reduction reaching 52% (Thune, Brenn, Lund, & Gaard, 1997), and 53-60% (Kruk & Aboul-Enein, 2003). There are studies, however, that report no relation between physical activity and risk (Coogan & Aschengrau, 1999; Dirx, Voorrips, Goldbohm, & van den Brandt, 2001; Dorgan et al., 1994), and others who report a non-significant decreased risk (Ueji, Ueno, Osei-Hyiaman, Takahashi, & Kano, 1998; Verloop, Rookus, van der Kooy, & van der Leeuwen, 2000). Several studies do show that household and outdoor chores are important factors in energy expenditure, and are large contributors to overall lifetime fitness (Ainsworth, Irwin, Addy, Whitt, & Stolarczyk, 1999; Friedenreich, Bryant, & Courneya, 2001; John, Horn-Ross, & Koo, 2003; Sternfeld, Ainsworth, & Quesenberry, 1999). Several different stances have been established with regard to when the optimal time for women to engage in physical activity as a protective role against breast cancer should take place. Some research has shown that when recreational activity is studied at different periods of a woman's life, a strong risk reduction is most evident from ages 14–20 years, and lessened at age 50 and above (Kruk, 2007). Other research demonstrates physical activity from sport, exercise, and household chores are breast cancer protective among adolescent and adult women (Matthews et al., 2001). Still, Friedenreich et al. (Friedenreich, Courneya, & Bryant, 2001) reports the strongest protection against breast cancer risk is when physical activity is performed later in life. Regardless of the stage in life, the importance of regular physical activity should be emphasized by all health professionals (e.g., physicians,

exercise physiologists, dietitians) as a means of protection against breast cancer, obesity, and the comorbidities that follow.

Many studies have looked at the effect of exercise on insulin-like growth factor and the binding proteins that regulate them (Rollison, Newschaffer, Tao, Pollak, & Helzlsouer, 2006; Schernhammer, Holly, Hunter, Pollak, & Hankinson, 2006; Schernhammer, Holly, Pollak, & Hankinson, 2005), with mixed results. It has been suggested that levels of IGF-1 (of the insulin-like growth factor family, which has been censured in cancer risk) and IGFBP-3 (a binding protein that controls IGF-1) in the body (International Agency for Research on Cancer, 2002; Yu & Rohan, 2000), have been altered by physical activity. Increased levels of IGF-1 and decreased levels of IGFBP-3 have been associated with a higher risk of breast, colon, and prostate cancer, however the evidence is not entirely conclusive (Pollak, Schernhammer, & Hankinson, 2004; Yu & Rohan, 2000). In a 12-week aerobic exercise training intervention, Campbell et al. reported a significant improvement in aerobic fitness and body composition (Campbell et al., 2007). The same study also revealed an association between an increase in lean body mass with a favorable change in the 2-OHE1 to 16 α -OHE1 ratio.

Importance of Exercise: Exercise and Cancer

It has been proposed that for our bodies to function in a normal, healthy fashion we must satisfy what our genes are programmed to expect of us – the maintenance of a normal physically active state, as adequate amounts of physical exercise help to maintain overall health (Booth et al., 2000). The sedentary lifestyle actually mimics a physiologically abnormal state, a concept which holds true for other mammals as well, where a study in laboratory rats describes a natural affinity to voluntarily exercise

(approximately 3 hours/day) if given an exercise running wheel, displaying a genetic disposition that is designed to anticipate physical exercise (Hamilton, Etienne, McClure, Pavey, & Holloway, 1998). As a result, chronic disease can be reduced considerably when physical activity becomes routine behavior, where Booth et al. contend that an active lifestyle can delay and even prevent early death, the need for medications, hospitalization, and other health care burdens (Booth et al., 2000).

A fundamental physiological understanding of how specific exercise mechanisms work will be important for the discovery of ways people can exercise toward health both efficiently and effectively (Booth et al., 2000). Proper exercise prescription plays an invaluable role in relation to overall health and wellness. Analyzing measurements of HRV, determining physiological thresholds, and implementing the results into clinical practice in both healthy and diseased groups may be advantageous and cost effective when establishing proper exercise prescription. Primary preventive medicine is underestimated too often, and the field of exercise physiology has an overwhelming amount of wealth to offer. The Centers for Disease Control and Prevention (1998) stated in a report that, “physical inactivity is one of the major underlying causes of premature mortality in the United States” (p. 1097) (Centers for Disease Control and Prevention, 1998), while Powell and Blair indicate sedentary living is responsible for approximately one-third of U.S. deaths, due to coronary heart disease, colon cancer, and type 2 diabetes – interestingly, all diseases wherein physical inactivity is an established primary causal factor (Powell & Blair, 1994). Several studies (Biewener & Bertram, 1994; Farrell et al., 1998; Vasankari, Kujala, Vasankari, & Ahotupa, 1998) have shown that consistent exercise training can prevent age-associated cardiovascular disease, diabetes,

hypertension, and osteoporosis. Additionally, appropriately performed exercise has even been described as a “magic bullet” because of its ability to positively impact so many risk factors for chronic disease, prevent and delay the onset of these diseases, and enhance longevity and quality of life (Booth et al., 2000).

Epidemiologic research examining the relationship between physical activity and breast cancer began approximately two decades ago (Frisch et al., 1985) and currently, there are over 65 epidemiologic cohort and case-control studies looking at this association. Strong epidemiological evidence exists in the association between increased physical activity and decreased risk of some cancers (Friedenreich & Orenstein, 2002; Lee, 2003), most notably colorectal and postmenopausal breast cancer, with a possible relation to endometrial, lung, and prostate cancer (Friedenreich & Orenstein, 2002). Among the modifiable factors that may play a key role in the primary prevention of breast cancer is an increase in physical activity and exercise (Bernstein et al., 1987; Matthews, 2004; Russell et al., 1984) where Dallal et al. reported on a long-term study of California teachers, revealing that strenuous long-term exercise activity has a protective role against invasive and in situ breast cancer (Dallal et al., 2007). The results of most studies provide evidence that an increased level of moderate to intense physical activity is linked to a decrease in risk of breast cancer, and the association itself has been evaluated several times (Friedenreich, 2004; Gotay, 2005; Kruk, 2005; Lagerros, Hsieh, & Asieh, 2004).

In a prospective study of women (Manson et al., 1999), a strong inverse relationship was found between energy expenditure and prevalence of coronary heart disease. In study participants who walked briskly for a minimum of 3 hours/week or

exercised vigorously for 1.5 hours/week, a 30-40% reduction in the risk of coronary heart disease was observed. In another prospective study of 21,000 male physicians (Manson et al., 1992), those who exercised enough to perspire 1 day/week were likely to develop type 2 diabetes 24% less than those who did not exercise. Additionally, if the frequency of this exercise were increased to 2-4 days/week, the prevalence of type 2 diabetes was reduced by 39%. The authors reported that benefits of exercise were most evident in the most obese physicians, and concluded that at least 25% of the incidence of type 2 diabetes may be attributed to a physically inactive lifestyle.

According to Campbell et al. a true understanding of the type, intensity, and duration of exercise necessary has not, however, been fully defined (Campbell & McTiernan, 2007). In trials of physical activity and weight loss, exercise groups typically experience a decrease in body weight, total body fat, intraabdominal and subcutaneous fat (Irwin et al., 2003), an increase in aerobic fitness (McTiernan et al., 2007), and also a reduction in insulin concentration, and improved insulin resistance (Frank et al., 2005) when compared with the control group (Irwin et al., 2003). Physical inactivity is an important risk factor in breast cancer, where increased activity over the course of a woman's lifetime is associated with a reduction in breast cancer risk (Kruk, 2007), a concept generally consistent with results of other studies (Bernstein et al., 1994; Dorn, Vena, Brasure, Freudenheim, & Graham, 2003; Lagerros et al., 2004).

An estimated 25% of cancer cases worldwide are caused by overweight or obesity and a sedentary lifestyle (International Agency for Research on Cancer, 2002), according to the International Agency for Research on Cancer. Currently, 36.5% of American adults are overweight, 25.1% are obese, and 22.6% report little or no physical activity (Centers

for Disease Control and Prevention). The review of Lagerros et al. (Lagerros et al., 2004) of four cohort and 19 case-control studies determined that exercise in adolescence and young adulthood is protective against breast cancer (a 20% decrease), while other studies (Bernstein et al., 2005; Carpenter, Ross, Paganini-Hill, & Bernstein, 1999; Verloop et al., 2000) did not classify a specific age or period in which the greatest breast cancer risk was reduced due to physical activity. Nevertheless, A reduced risk of breast cancer among younger women (age \leq 40 years) who exercised a minimum of 3.8 hours/week, was revealed by Bernstein et al. (Bernstein et al., 1994), which is consistent with the work of Dorn et al., in which women who were involved in physical activity at least 20 years prior to the study interview displayed strong protective effects against breast cancer (Dorn et al., 2003). In contrast however, Lee et al. revealed no effect of lifetime recreational activity on breast cancer risk during any time periods of a woman's life (Lee, Cook, Rexrode, & Buring, 2001). This is consistent the findings of a cohort study in Norwegian-Swedish women in which no indication of breast cancer protection by way of physical activity was evident when measured in 14 and 30 year olds (Margolis et al., 2005). Studies have shown, however, that physical activity and diet are difficult measures to evaluate with great accuracy, precise determinations of body composition in large groups are difficult, and the origin of cancer is often multifactorial (Friedenreich, Thune, Brinton, & Albanes, 1998; Hofman-Getz et al., 1998; Rundle, 2005). Cancer also has a latency period that makes it difficult to study these associations because it is often many years between critical exposure and actual disease diagnosis (Campbell & McTiernan, 2007).

Kruk et al. determined that exercise activity between ages 14 and 20 years had the greatest association with breast cancer risk, and that the largest risk reduction (72%) was found when information on all types of activity was combined and physical activity was measured in hours/week/year (Kruk, 2007). This is consistent with the findings of Marcus et al., implying exercise in adolescence and youth may have a protective role against adult breast cancer (Marcus et al., 1999). In their review, Kruk et al. contends that the Pearson correlation coefficient between activity at age 14–20 years and at age above 20 years was 0.31, and in the same way, the low correlations were observed for lifetime activity measures and time periods measures overall and for cases and controls, separately (from 0.06 to 0.23) (Kruk, 2007). Using a similar measurement of activity, MET- hours/week/year, Friedenreich et al. stratified participants into quartiles of combined household, occupational and recreational activities (Friedenreich, Bryant et al., 2001). This study revealed a reduced risk of breast cancer related to lifetime total physical activity in post-menopausal women only, where risk reduction in that study was attributable to physical household and occupational physical activities. John et al. also reported a decreased risk of breast cancer risk among both pre- and post-menopausal women (John et al., 2003). A recent study utilizing current, rather than lifetime, physical activity data from different sources of exercise (household, recreational, walking, stairs), supported the relationship that links physical activity to breast cancer risk (Tehard, Friedenreich, Oppert, & Clavel-Chapelon, 2006), where researchers found the largest risk reduction in those who reported vigorous recreational activity, compared with those who reported no recreational activity.

Biomedical exercise research has the potential to affect millions of people and may help change the scientific community's mistaken views on exercise physiology. Many identify exercise physiology as a field that exclusively studies elite-level athletes, when in fact an overwhelming majority of exercise-related research is not based in the field of athletic performance, rather in the health sciences. The Centers for Disease Control and Prevention declared that premature mortality in the U.S. may be due in large part to increasingly physically inactive lifestyles (Centers for Disease Control and Prevention, 1998), and although it is naïve to believe all diseases would simply disappear if every person simply exercised more, it is essential to explore the physiological markers that may aid in the intervention of physical inactivity. Considering this, determining if a HRVT exists (and can identify other important physiological thresholds) may help in the foundation of non-invasive measurements in individualized exercise prescription.

CHAPTER 3 METHODOLOGY

Study 1

The first study was designed to determine if changes in heart rate variability during incremental exercise can be used to identify lactate threshold and ventilatory threshold in healthy adults.

Participants

Twenty-eight volunteers between 18 and 42 years of age were recruited by word of mouth. The sample had a wide range of aerobic capacities and fitness levels, but none were college athletes. University Internal Review Board approval was obtained and all participants provided written informed consent in accordance with the guidelines established by the Human Investigations Committee of the university. Complete data was not collected on four participants, thus results are reported on 24 participants (9 males/15 females).

Exercise Testing Protocol

Participants were instructed to avoid alcohol the evening before testing and remain fasting after 10 p.m. Studies were initiated at 8 a.m. the following morning. Upon arrival to the laboratory, height, weight and body fat were assessed using a stadiometer (SECA, Model 220, Hamburg, Germany), physician scale (SECA, Model 710, Hamburg, Germany), and air plethysmography (Life Measurement Inc., Model 2000A, Concord, CA, USA) (Fields, Goran, & McCrory, 2002), respectively. Participants were then familiarized with the exercise testing equipment and procedures.

A continuous graded protocol was used for exercise testing on a mechanically braked cycle ergometer (Monark, Model 818, Varberg, Sweden) which was calibrated

before each test. The testing consisted of 3 minute stages (Dickhuth et al., 1999; Tulppo et al., 1998), allowing more stability of RR intervals, and began with the participant resting on the bike, with no pedaling as a baseline rest. Pedaling began at the second stage, at which exercise intensity started at 25 Watts (W). Every 3 minute, intensity increased at 25W increments. Participants were instructed to maintain a cycling speed of 50 revolutions per minute. Exercise test time ranged from 15 to 35 minute, depending on the participant's exercise capacity. All participants ended the test when they reached volitional fatigue.

Metabolic Measures

Respiratory gas exchange was measured continuously by open circuit spirometry indirect calorimetry using a metabolic cart (Sensor Medics Corp., 229L metabolic gas analyzer, Yorba Linda, CA, USA) and was measured using 20 second averages. Prior to each test, oxygen and carbon dioxide analyzers were calibrated with a medical gas mixture of known composition. Mass flow sensor calibration with a 3-liter syringe (Sensor Medics Corp., 3L Calibrated Syringe-D, Yorba Linda, CA, USA) was performed before each test.

Heart Rate

A Polar[®] heart rate monitor (Polar, Vantage XL, Woodbury, NY, USA) was used to record the participant's RR intervals (beat to beat fluctuation of HR) throughout the test. The RR interval data were stored in the receiving watch, then uploaded to a computer for analysis.

Assessment of Lactate Threshold and Blood Lactate Concentrations

Blood lactate values were obtained via a finger prick capillary blood sample (25 μ L) immediately before each testing protocol, and were then collected at the end of each 3 minute exercise stage. “Peak” blood lactate values were taken 3 minute post exercise (Koziris & Montgomery, 1991). Samples were analyzed immediately for whole blood lactic acid concentration (mmol/L) using a standard enzymatic method on a YSI 1500L lactate analyzer (YSI, Yellow Springs, OH, USA).

Determination of Ventilatory Threshold (VT)

Three methods to determine VT were evaluated concurrently to determine VT using procedures described previously (Gaskill et al., 2001). These methods include the ventilatory equivalent method, the excess carbon dioxide method, and the modified V-slope method which was modified from the original method (Beaver et al., 1986), which used breath-by-breath gas analysis of 20 second gas collection averages.

Determination of Lactate Threshold (LT)

Lactate threshold was defined as the first rise in blood lactate from low-intensity, steady state exercise (Gaskill et al., 2001). Blood lactate values were then graphically plotted against VO_2 . A visual interpretation was independently made of each graph by two trained researchers to locate the first rise from baseline. A third researcher adjudicated any differences by independently determining VT, which occurred on four occasions. The three evaluators then jointly agreed on the LT point.

Determination of Heart Rate Variability Threshold (HRVT)

The RR intervals from the last 2 minutes of rest and each stage of exercise were used for analysis of HRV. After the RR intervals were separated by stage, the data were

filtered automatically to remove missing or premature beats. An RR interval was interpreted as a premature beat if it deviated from the previous qualified interval by >30% (Tulppo et al., 1998). The data were also visually inspected. There are a variety of indices that have been used to assess HRV, which can be divided into 2 major categories: time domain indexes and frequency domain indexes. Time domain indexes such as SD and MSD, the mean absolute difference between consecutive RR intervals, have been shown to correlate well with vagal tone ($r = 0.87$ and 0.92 respectively; $p < 0.001$): just as frequency domain indexes such as the high-frequency component calculated by autoregressive spectrum analysis and fast Fourier transform (Hayano et al., 1991). As a result, the time domain indexes of SD and MSD were chosen as the HRV indices for use in this investigation.

To determine the HRVT, the MSD and SD of HR intervals for each stage of exercise were graphically plotted against work rate (Figures 1, 2). Then, in a manner similar to the determination of LT, a visual interpretation was made to locate the point at which there was no further decline in HRV, thus indicating vagal withdrawal. Thus, this HRV deflection point was defined as the HRVT.

Statistical Analysis

Participant data were analyzed using statistical procedures. Analysis of variance (ANOVA) was used to test the statistical significance of the differences among the mean values of ventilatory, lactate, and HRV thresholds in SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Levene's test for homogeneity of variance was used. Significant effects were followed up by Duncan's multiple range test for post hoc comparisons. Pearson product moment correlation was used to demonstrate the respective correlations

between the oxygen consumption at which VT occurs (VO_2^{vt}), the oxygen consumption at which LT occurs (VO_2^{lt}), and the oxygen consumption at which HRVT occurs ($\text{VO}_2^{\text{hrvt}}$). In addition, the methods of Bland and Altman (Bland & Altman, 1986) were used to assess similarities between VT, LT, and HRVT (Figure 3). Bland-Altman pairwise comparisons evaluate the validity of one method to an accepted technique. Validity of a new method may decrease if 1) the mean difference is greater than the total technical error, 2) the plot shows data points outside the confidence intervals, and 3) there is a significant relationship (one method will then over or underestimate the other as a function of size). This comparison is a graphical representation of the difference (absolute or % change of accepted) between methods and the average of these methods.

The use of HRVT to estimate LT was determined by evaluating mean differences and SD of the differences between tests. This method was used to compare BLA measurements and the MSD and SD of HRV for each stage of exercise. The VO_2 value at which LT took place for each participant, corresponding to stage of exercise, was compared to the stage of exercise in which HRVT took place (Figures 1, 2). The Null hypothesis for this study was $H_0: \mu_{\text{VT}} \neq \mu_{\text{LT}} \neq \mu_{\text{HRVT}}$. The Alternative hypothesis was $H_a: \mu_{\text{VT}} = \mu_{\text{LT}} = \mu_{\text{HRVT}}$. Hypotheses were tested with nominal α set to 0.05.

Study 2

The second study was designed to determine the influence of caffeine on ventilatory, lactate, and HRV thresholds during progressive exercise in normal healthy participants.

Preliminary Procedures

Ten college students (4 females, 6 males) participated in this study after providing written informed consent in accordance with the guidelines established by the Human Investigations Committee of the university, which approved the study. A preliminary meeting served to review medical history and assure the current health status of each participant. Volunteers with contraindications to strenuous exercise testing were excluded from participation. Similarly, individuals with habitual caffeine consumption exceeding $300 \text{ mg}\cdot\text{day}^{-1}$ were also excluded (Engels & Haymes, 1992). For that purpose, an updated version of an established habitual caffeine intake questionnaire (Engels, Wirth, Celik, & Dorsey, 1999) was used to determine the typical daily caffeine intake of volunteers on two separate occasions at the beginning of the study. Participants were instructed to refrain from alcohol and caffeine containing products for 24 hours prior to testing (Blanchard & Sawers, 1983).

Experimental Protocol

Each experimental test occurred in the morning, following a 10 hour overnight fast. Adherences to these requests were verified by questionnaire. Height, weight and body composition were assessed using a stadiometer (SECA, Model 220, Hamburg, Germany), physician scale (SECA, Model 710, Hamburg, Germany), and air plethysmography (Life Measurement Inc., Model 2000A, Concord, CA, USA) (Fields et al., 2002), respectively. Measurements were obtained on the first visit, served descriptive purposes, and established individual caffeine dosage levels. Participants were familiarized with the exercise testing procedures. Each participant completed two trials under controlled laboratory conditions, one with caffeine ingestion and one with placebo.

The study was a randomized, placebo controlled, double-blind design, where 4 to 7 days separated each of the two test sessions. Sixty minutes prior to exercise testing, participants ingested either $5 \text{ mg}\cdot\text{kg}^{-1}$ body weight (Blanchard & Sawers, 1983; Bond et al., 1987; Powers et al., 1983) of anhydrous caffeine (Firma Caesar & Loretz, Hilden, Germany), which was dissolved in 250 ml of caffeine-free diet cola, or the placebo, which was the same caffeine-free diet cola without the added caffeine. Participants then rested quietly in the laboratory until data acquisition began.

A continuous graded protocol was used for exercise testing on a calibrated, mechanically braked cycle ergometer (Monark, Model 818, Varberg, Sweden). Testing began with the participant resting on the bike, without pedaling, as baseline values were collected for 3 minutes. Exercise began at the second stage, where pedaling intensity initiated at 25W, and increased at 25W increments at every 3 minute stage (Dickhuth et al., 1999; Powers et al., 1983; Tulppo et al., 1998), thus allowing for stability of RR intervals. Participants were instructed to maintain a cycling speed of 50 revolutions per minute throughout the exercise protocol. All participants ended the test when they reached volitional fatigue.

Metabolic Measures

Respiratory gas exchange of VO_2 , carbon dioxide output (VCO_2), and expired ventilation (V_E) were measured continuously by open circuit spirometry indirect calorimetry using a metabolic cart (Sensor Medics, 229L Metabolic Gas Analyzer, Yorba Linda, CA, USA) and were measured using 20 second averages. Prior to each test, oxygen and carbon dioxide analyzers were calibrated with a medical gas mixture (Viasys Healthcare, Gas, 4% CO_2 , 16% O_2 , Bal. N_2 , Palm Springs, CA, USA). In addition, mass

flow sensor calibration with a 3-liter syringe (SensorMedics Corp., 3L Calibrated Syringe-D, Yorba Linda, CA, USA) was performed prior to each test.

Heart Rate

A Polar ® HR monitor (Polar, Vantage XL, Woodbury, NY, USA) was used to record RR intervals throughout the test to an accuracy of 1 ms (digitized signal at 1000 Hz). The RR interval data were stored in a receiving watch, and subsequently uploaded to a computer for analysis.

Blood Lactate Concentration

Capillary blood samples (25uL) were obtained via finger prick to establish BL_a values at rest, during the last 30 seconds of each exercise stage, and 3 minute post-exercise to determine “peak” BL_a value (Koziris & Montgomery, 1991). Aliquots were immediately analyzed for whole BL_a concentration ($\text{mmol}\cdot\text{L}^{-1}$) using a standard enzymatic method on a YSI 1500L lactate analyzer (YSI, Yellow Springs, OH, USA).

Determination of Ventilatory, Lactate, and Heart Rate Variability Thresholds

Ventilatory and lactate thresholds were determined according to Gaskill (Gaskill et al., 2001). Briefly, VT was established by three techniques; including the ventilatory equivalent method, excess carbon dioxide method, and the modified V-slope method using breath-by-breath gas analysis of 20 second gas collection averages. Lactate threshold was defined as the first rise in BL_a from low-intensity, steady state exercise (Gaskill et al., 2001) where BL_a values were plotted against VO_2 .

The HRVT was determined by using the time domain indices SD, CV, and MSD, which have been shown to correlate well with vagal tone ($r = 0.87, 0.81, \text{ and } 0.92$ respectively; $p < 0.001$); just as the frequency domain indices of autoregressive spectrum

analysis. The RR intervals from the last 2 minute of rest and each stage of exercise were used for analysis of HRV. Data were separated by stage, and automatically filtered to eliminate missing or premature beats. RR intervals were designated premature beats if they deviated from the previous eligible interval by $> 30\%$ (Tulppo et al., 1998).

To determine HRVT during graded exercise testing, time domain indices of HR intervals for each stage of exercise were graphically plotted against work output (W) (Figure 6). Then, in a manner similar to the determination of LT and VT, a visual interpretation was made to locate the point at which there was no further decline in HRV, thus indicating vagal withdrawal. This HRV deflection point was defined as the HRVT.

Visual interpretations of each graph were independently made by two trained researchers to locate the respective thresholds. A third researcher adjudicated any differences by independently determining the thresholds. If an agreement could not be made, the data were rejected.

Statistical Analysis

Participant data were analyzed using statistical procedures. Caffeine versus placebo data were analyzed using one-way repeated measures ANOVA. Mauchly's Test of Sphericity was used to demonstrate homogeneity of variance. Significant effects were followed up by Student-Newman Keuls, and the two tailed t -test for post hoc comparisons. The study was a within-participants design, where each participant served as her/his own control for the test-retest procedure. Pearson's correlation was used to demonstrate the respective correlation between the oxygen consumption at which HRVT occurred for CV, SD and MSD. The Null hypothesis for this study was $H_0: \mu_{PLCBTHRSH} \neq$

$\mu_{\text{CAFFTHRSH}}$. The Alternative hypothesis was $H_a: \mu_{\text{PLCBTHRSH}} = \mu_{\text{CAFFTHRSH}}$. Hypotheses were tested with nominal α set to 0.05.

Study 3

The third study was designed to measure the LT, VT and HRV response to progressive exercise in obese African American breast cancer survivors.

Participants

Fifty-three female African American breast cancer survivors (55.58 ± 7.57 y; 164.01 ± 5.94 cm; 88.21 ± 13.79 kg; 42.02 ± 4.17 % body fat) participated in the study. Body composition was determined using dual energy x-ray absorptiometry (QDR 4500 Acclaim Series Elite, Hologic Inc., Bedford, MA, USA). Written informed consent was obtained prior to participation in the study, in accordance with the Human Investigation Committee of the University. At the time of evaluation, participants were diagnosed with stage I, II, or IIIA breast cancer less than 3 years prior, and were greater than 3 months post chemo or radiation therapy.

Study Protocol

Participants arrived at the laboratory the morning after an overnight fast. Prior to the exercise test participants were familiarized with the testing procedure which consisted of a continuous graded protocol on a stationary cycle ergometer (Monark, Model 818, Varberg, Sweden). Each stage of exercise was 3 minute in duration (Dickhuth et al., 1999; Powers et al., 1983; Tulppo et al., 1998), thus allowing for stability of RR intervals. Stage 1 of the protocol began with the participant resting on the bike, without pedaling, while basal values were collected. Exercise commenced in stage 2 where pedaling began at 25W, and stage increments increased at 25W thereafter. Exercise tests

were terminated (1) when a pedaling frequency of 50 rpm was not maintained, (2) voluntarily by the participants, (3) when participants reached 85% of their heart rate reserve (Young-McCaughan & Arzola, 2007), or (4) when the respiratory exchange ratio exceeded 1.1.

Blood Lactate and Determination of LT

An antecubital intravenous catheter was used to collect serial blood samples for the measurement of BLa at rest, and initially in the last 20 seconds of each 3 minute stage. Subsequently, it was determined that one blood sample for each stage of exercise was inadequate; therefore blood samples were collected during the last 20 seconds of each minute for the last 10 participants. A final blood sample was collected at 3 minutes post-exercise to determine “peak” BLa value (Koziris & Montgomery, 1991). Samples were immediately put on ice, centrifuged, then stored at -70°C for analysis of plasma BLa concentration ($\text{mmol}\cdot\text{L}^{-1}$) using a standard enzymatic method on a YSI 1500L lactate analyzer (YSI, Yellow Springs, OH, USA). The LT was determined by the rise in BLa concentration from the low values at rest and during low-intensity exercise. Blood lactate values were graphically plotted against VO_2 (Figure 10).

Metabolic Measurements and Determination of VT

Respiratory gas exchange was measured continuously by open circuit spirometry indirect calorimetry using a metabolic cart (AMETEK, oxygen analyzer S-3A/I, carbon dioxide analyzer CD-3A, Pittsburgh, PA, USA). Calibration of instrumentation was done before each test. The VT was determined using the ventilatory equivalent method, as measured by a rise in the ventilatory equivalent of oxygen (V_E/O_2) without a concurrent rise in the ventilatory equivalent of carbon dioxide (V_E/CO_2) (Wasserman, Hansen, Sue,

& Whipp, 1987) and a modification of the V-slope method (Gaskill et al., 2001) which was modified from the original procedures (Beaver et al., 1986; Wasserman et al., 1987) and used breath-by-breath gas analysis of 20 second gas collection averages (Figure 11).

Heart Rate Variability Instrumentation and Determination of HRVT

Throughout each test RR interval recordings were made with a Polar ® heart rate monitor (Polar, S810i, Woodbury, NY, USA) to an accuracy of 1 ms. The RR interval data were stored in a receiving watch, and later uploaded to a computer for analysis. For examination of HRV, RR intervals were separated into 20 second increments. To remove missing or premature beats, the data were filtered automatically. An RR interval was considered premature if it deviated from the previous qualified interval by > 30% (Tulppo et al., 1998). The data were also visually inspected.

The HRV time domain indices of SD, CV, and MSD were chosen for use in this investigation (Hayano et al., 1991). Time domain indices were plotted against time and oxygen consumption (Figures 12, 13), and the HRVT deflection point was established using a visual interpretation method similar to the one used to determine VT. A deflection point was located at which there was no further decline in HRV, an indication of vagal withdrawal, and thus was defined as the HRVT.

Statistical Analysis

Participant data were analyzed using statistical procedures. Analysis of variance was used to test the statistical significance of the differences among the mean values of HRV time domain indices (SD, CV, MSD). Analysis of variance was also used to test the statistical significance of the differences among the mean values of ventilatory, lactate, and heart rate variability thresholds. Levene's test for homogeneity of variance was used

prior to conducting each ANOVA. Significant effects were followed up by Duncan's multiple range test for post hoc comparisons. Pearson's correlation was used to demonstrate the respective correlations between the oxygen consumption at which VT, LT and HRVT occurred. In addition, the methods of Bland and Altman (Bland & Altman, 1986) were used to assess similarities between VT, LT, and HRVT. The Null hypothesis for this study was $H_0: \mu_{VT} \neq \mu_{LT} \neq \mu_{HRVT}$. The Alternative hypothesis was $H_a: \mu_{VT} = \mu_{LT} = \mu_{HRVT}$. Hypotheses were tested with nominal α set to 0.05.

CHAPTER 4 RESULTS

Study 1

The results of the first study in determining if changes in HRV during incremental exercise can be used to estimate LT and VT in healthy adults are as follows. Descriptive data are shown in Table 1. Analysis of variance revealed a non-significant difference ($F(df = 2, 69) = 0.39, p = 0.18$) for the oxygen consumption at which VT occurred (VO_2^{vt}), the oxygen consumption at which LT occurred (VO_2^{lt}), and the oxygen consumption at which HRVT occurred (VO_2^{hrvt}). On average, participants who reached higher VO_2 peaks (2.1 – 3.9 L/min) had higher VO_2^{vt} (1.5 – 2.4 L/min) and VO_2^{lt} (1.6 – 2.3 L/min) values. Work output level at which HRVT was determined based on MSD and SD of RR intervals can be seen in Figures 1 and 2.

The plots in the left panel of Figure 3 graphically display the respective correlations between VT, LT, and HRVT. The Bland-Altman plots are seen in the right panel where a line of best fit is indicated, and dark lines are provided at ± 3 SD on each graph. The mean of VO_2^{vt} and VO_2^{lt} for each participant was plotted against the difference between the VO_2^{vt} and VO_2^{lt} in the Bland-Altman plot of Figure 3 (top right), which illustrates good agreement. The mean VO_2^{vt} and VO_2^{lt} was 1.43 ± 0.46 (L/min). Likewise, the mean of VO_2^{hrvt} and VO_2^{lt} for each participant was plotted against the difference between the VO_2^{hrvt} and VO_2^{lt} in the Bland-Altman plot of Figure 3 (middle right), which also illustrates good agreement. The mean VO_2^{hrvt} and VO_2^{lt} was 1.40 ± 0.46 (L/min). Finally, the mean of VO_2^{hrvt} and VO_2^{vt} for each participant was plotted against the difference between the VO_2^{hrvt} and VO_2^{vt} in the Bland-Altman plot of Figure 3

(bottom right), which illustrates good agreement as well. The mean $\text{VO}_2^{\text{hrvt}}$ and VO_2^{vt} was 1.46 ± 0.45 (L/min).

The results for the determination of HRVT during incremental exercise testing, using RR interval data, showed similarities in VO_2 (L/min) values between LT detection and HRVT detected by HRV deflection point. The mean difference between $\text{VO}_2^{\text{hrvt}}$ and VO_2^{lt} was not significant (F (df = 1, 46) = 0.93, p = 0.34). A good correlation between VO_2 values for LT and HRVT was observed (r = 0.82) in Figure 3 (middle left). The mean difference between $\text{VO}_2^{\text{hrvt}}$ and VO_2^{vt} was also not significant (F (df = 1, 46) = 1.95, p = 0.18). A good correlation between $\text{VO}_2^{\text{hrvt}}$ and VO_2^{vt} was also detected (r = 0.89) in Figure 3 (bottom left).

TABLE 1. Descriptive data of *Study 1* participants (means \pm SD).

	male (n=9)	female (n=15)
Age (y)	26.8 \pm 7.0	24.7 \pm 7.5
Height (cm)	176.0 \pm 7.1	164.8 \pm 6.5
BM (kg)	74.7 \pm 7.5	66.3 \pm 12.4
LBM (kg)	66.1 \pm 7.3	47.0 \pm 7.4
FBM (kg)	8.5 \pm 4.4	19.3 \pm 6.8
Body fat%	11.6 \pm 5.8	28.4 \pm 7.1
Basal lactate (mmol/L)	1.0 \pm 0.2	1.2 \pm 0.2
Blood lactate at LT (mmol/L)	3.8 \pm 1.3	3.0 \pm 1.4
Blood lactate at peak (mmol/L)	11.7 \pm 1.9	10.3 \pm 2.3
VO_2^{lt} (L/min)	1.8 \pm 0.4	1.1 \pm 0.3
VO_2^{vt} (L/min)	1.9 \pm 0.4	1.3 \pm 0.3
$\text{VO}_2^{\text{peak}}$ (L/min)	2.9 \pm 0.6	1.8 \pm 0.4
RER at $\text{VO}_2^{\text{peak}}$	1.1 \pm 0.1	1.1 \pm 0.04

FIGURE 1. Visual detection of HRVT (HRV deflection point indicated by the arrow) using the MSD method, which was calculated for each stage of exercise.

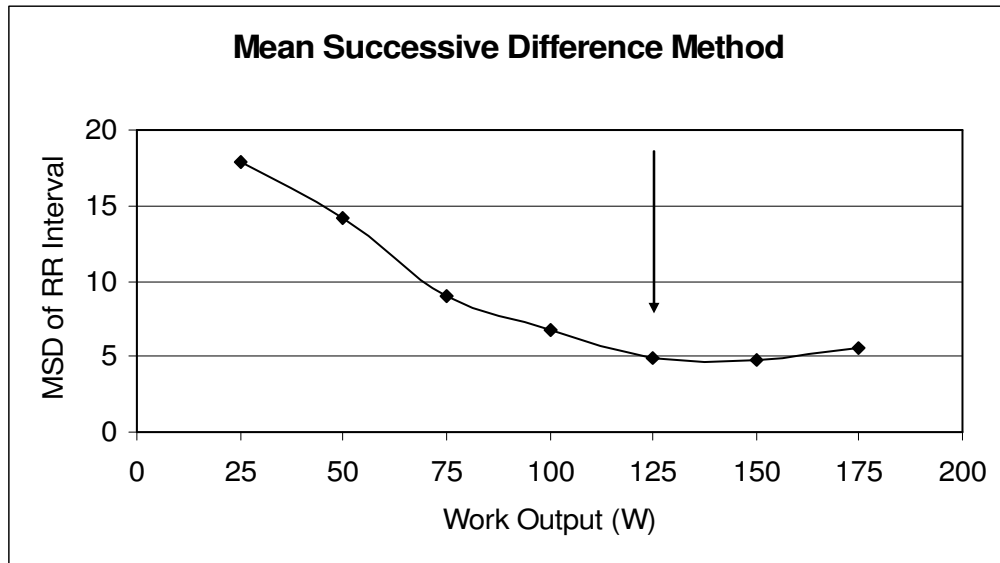


FIGURE 2. Visual detection of HRVT (HRV deflection point indicated by the arrow) using SD method. The SD of RR intervals was calculated and plotted for each stage of exercise.

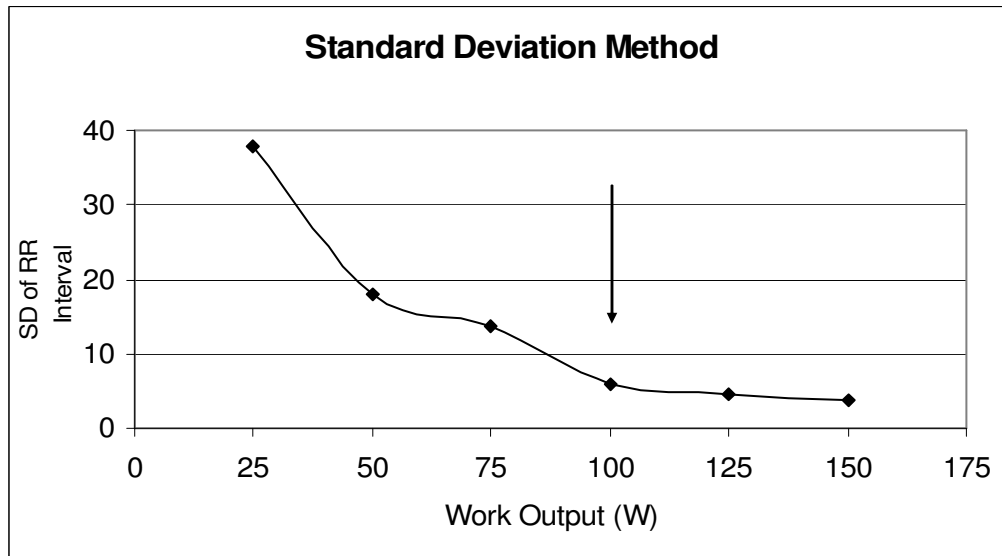
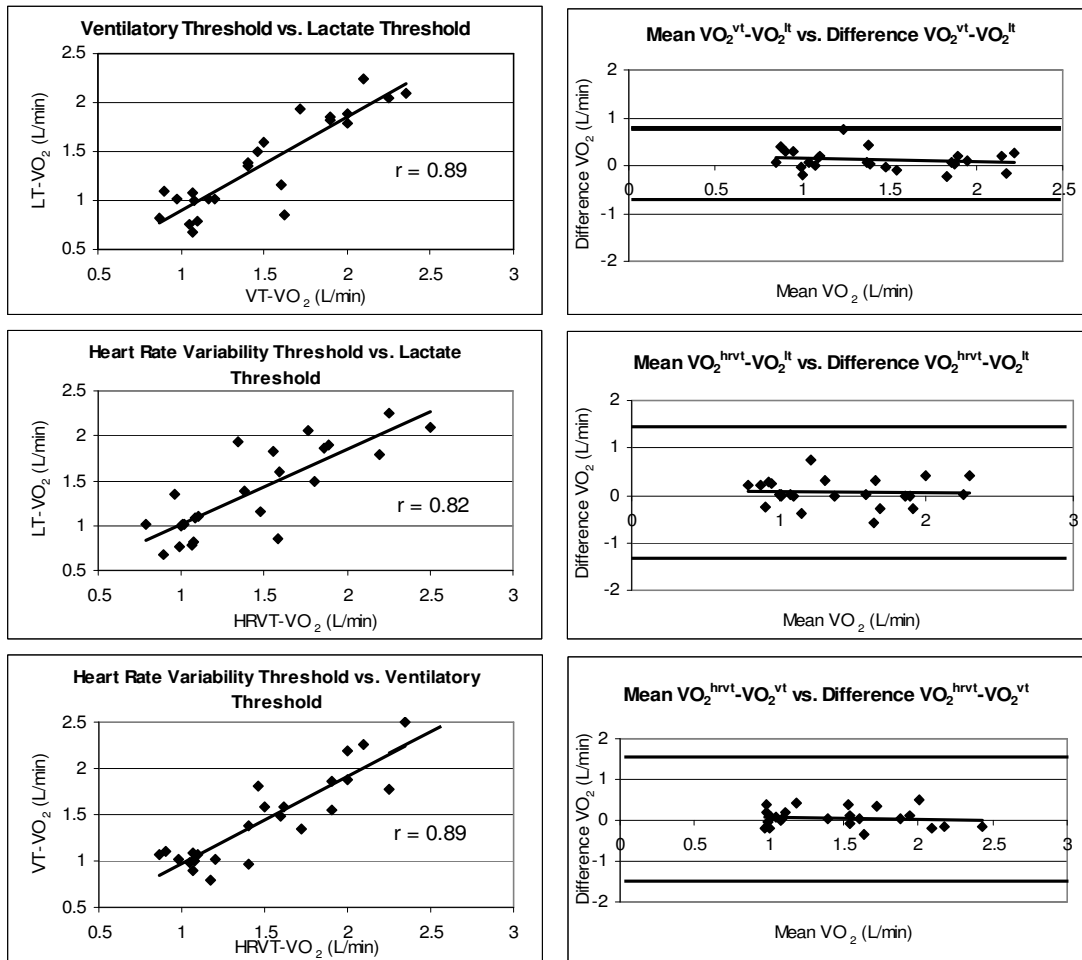


FIGURE 3. Validity testing of VO_2^{vt} , VO_2^{lt} , and $\text{VO}_2^{\text{hrvt}}$. The *left panel graphs* show the relationship of VO_2^{vt} vs. VO_2^{lt} , $\text{VO}_2^{\text{hrvt}}$ vs. VO_2^{lt} , and $\text{VO}_2^{\text{hrvt}}$ vs. VO_2^{vt} with a line of best fit and correlation coefficient (r) shown on each graph. The *right panel graphs* are Bland-Altman plots. These graphs plot the respective difference between VO_2^{vt} , VO_2^{lt} and $\text{VO}_2^{\text{hrvt}}$ (y-axis) for each individual against the means of VO_2^{vt} and VO_2^{lt} , $\text{VO}_2^{\text{hrvt}}$ and VO_2^{lt} , and $\text{VO}_2^{\text{hrvt}}$ and VO_2^{vt} .

The *dark lines* in each Bland-Altman plot represent ± 3 SD. Note that most data points fall within ± 2 SD from the mean (0.32 and -0.56 , for VO_2^{vt} and VO_2^{lt}), (1.01 and -0.90 , for $\text{VO}_2^{\text{hrvt}}$ and VO_2^{lt}), and (0.99 and -0.86 , for $\text{VO}_2^{\text{hrvt}}$ and VO_2^{vt}) and almost all data points fall within ± 3 SD from the mean, which displays a strong agreement between the various methods.



Study 2

The results of the second study of the dissertation in determining the influence of caffeine on lactate, ventilatory, and heart rate variability thresholds during progressive exercise are as follows. Participant descriptive data are shown in Table 2. The BL_a, VO₂, HR, and V_E comparisons of placebo and caffeine trials are shown in Table 3. Caffeine consumption of 5 mg·kg⁻¹ body weight significantly (F (df = 1, 18) = 7.17, p = 0.028) increased mean VO₂ (3.79 ± 0.93 to 4.39 ± 1.08 ml·kg⁻¹·min⁻¹) at rest. Caffeine consumption also significantly (F (df = 1, 18) = 6.71, p = 0.032) increased mean VCO₂ (3.34 ± 0.98 to 4.07 ± 0.79 ml·kg⁻¹·min⁻¹) at rest. Caffeine consumption did not, however, have a significant effect on mean exercise VO₂ or VCO₂ values (p > 0.05). Caffeine consumption also significantly increased BL_a at rest (F (df = 1, 18) = 15.52, p = 0.003) (Figure 4), but did not impact BL_a values during graded exercise (Table 3). Measurements of resting HR were not significantly different in the placebo compared to the caffeine trial (Table 3, Figure 5). The HRV index of CV was significantly increased (F (df = 1, 18) = 6.71, p = 0.029) with caffeine at rest (0.08 ± 0.02 vs. 0.10 ± 0.02), while values of SD (66.75 ± 27.33 vs. 77.90 ± 25.46) and MSD (36.75 ± 27.73 vs. 38.20 ± 19.95), though not significant, were also increased with caffeine consumption at rest (Figures 6, 7). Caffeine significantly increased resting minute ventilation (V_E) volumes (F (df = 1, 18) = 9.99, p = 0.013), as well as V_E volumes at VT (F (df = 1, 18) = 13.43, p = 0.006) (Table 3). Ventilatory equivalents of V_E/VO₂ and V_E/VCO₂ were not significantly different (Figure 8). Despite differences at rest, placebo and caffeine trial measurements of VO₂, BL_a, HR, and HRV were not significantly different during exercise. Placebo versus caffeine trial LT, VT and HRVT were also not significantly different (p > 0.05)

(Table 3). An example of a typical HRV and BLa response pattern during progressive exercise during the caffeine trial is shown for one participant (Figure 9), where the threshold is indicated.

The results for the determination of HRVT during graded exercise testing, using RR interval data, were established by comparing VO_2 ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) to the respective indices of HRV (Figure 7). Upon initiation of exercise, all HRV index values began to decline, reaching a mean deflection point at $19.09 \pm 4.51 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ in the placebo trial and $19.54 \pm 4.62 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ in the caffeine trial. These means displayed a good correlation ($r = 0.98$) and non-significant difference between trials and were determined to be the HRVT (Table 3). When the respective HRV indices were compared to stages of work output (W) the agreement between all three HRV indices occurred at 100W, despite caffeine ingestion, where little further decline in HRV took place thereafter (Figure 6).

TABLE 2. Descriptive data of *Study 2* participants (mean \pm SD).

Age (y)	25.60 ± 7.12
Height (cm)	170.40 ± 9.66
Body Weight (kg)	69.32 ± 13.83
Body Fat (%)	17.22 ± 9.81

TABLE 3. Blood lactate (BLa), oxygen consumption (VO_2), heart rate (HR), and expiratory ventilation volumes (V_E) at rest, threshold, and peak measurements (mean \pm SD). * $p < 0.05$

	Placebo	Caffeine
BLa at rest ($\text{mmol}\cdot\text{L}^{-1}$)	1.01 \pm 0.24	* 1.51 \pm 0.46
BLa at VT ($\text{mmol}\cdot\text{L}^{-1}$)	3.88 \pm 2.27	4.85 \pm 2.53
BLa at Peak ($\text{mmol}\cdot\text{L}^{-1}$)	11.09 \pm 2.10	11.81 \pm 1.68
VO_2 at rest ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	3.79 \pm 0.93	* 4.39 \pm 1.08
VO_2 at LT ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	18.74 \pm 4.42	18.59 \pm 5.07
VO_2 at VT ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	18.67 \pm 4.36	18.57 \pm 5.04
VO_2 at HRVT ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	19.09 \pm 4.51	19.54 \pm 4.62
VO_2 max ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	35.53 \pm 9.85	35.56 \pm 8.25
HR at rest (bpm)	78.07 \pm 16.70	79.86 \pm 13.91
HR at VT (bpm)	139.17 \pm 35.30	138.62 \pm 29.26
HR at max (bpm)	180.15 \pm 18.28	180.65 \pm 13.13
V_E at rest ($\text{L}\cdot\text{min}^{-1}$)	10.81 \pm 3.18	* 12.87 \pm 2.74
V_E at VT ($\text{L}\cdot\text{min}^{-1}$)	37.82 \pm 4.11	* 41.17 \pm 5.01
V_E at max ($\text{L}\cdot\text{min}^{-1}$)	89.86 \pm 32.13	98.31 \pm 32.51

FIGURE 4. Plot of oxygen consumption ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) versus blood lactate (mean \pm SD). A significant difference ($p < 0.05$) is observed at rest, but as exercise intensity increases, caffeine fails to display a significant impact. Arrow and inset values indicate the VO_2 value at which LT occurred in placebo and caffeine trials.

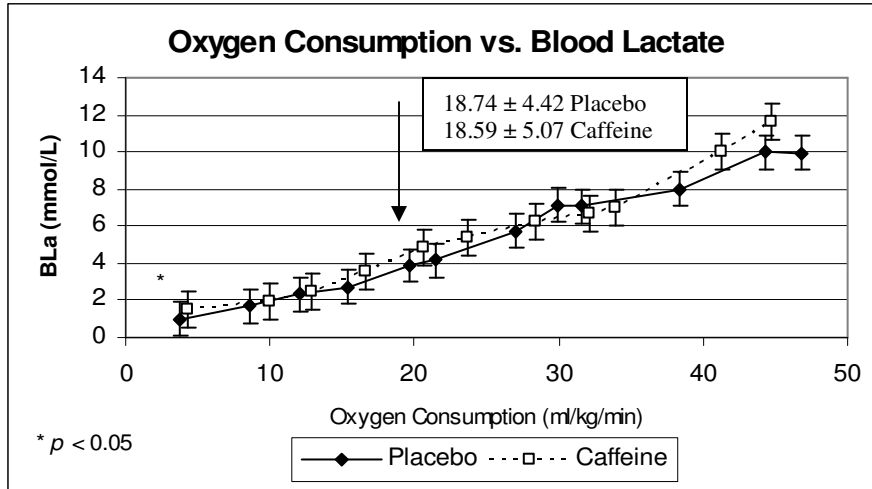


FIGURE 5. Plot of oxygen consumption ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) versus heart rate (mean \pm SD).

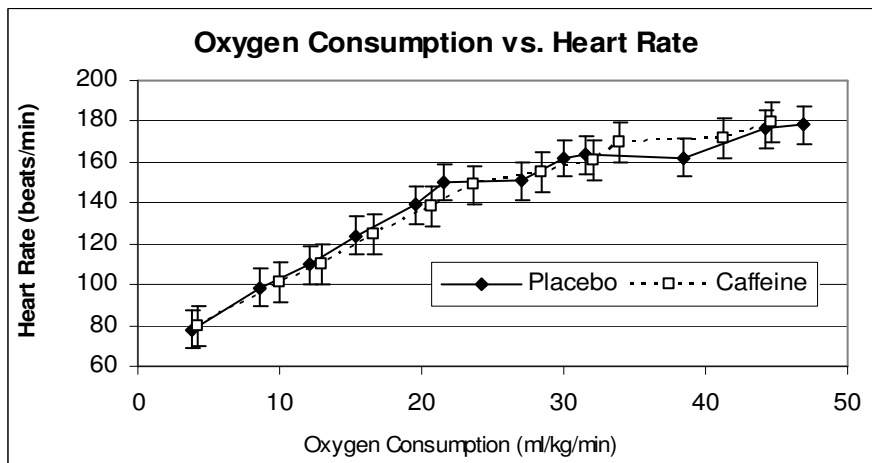


FIGURE 6. Heart Rate Variability Threshold. HRVT is defined via three different measurements (CV, SD, MSD) versus work output (W). Arrow indicates the point at which vagal withdrawal occurred (100 W).

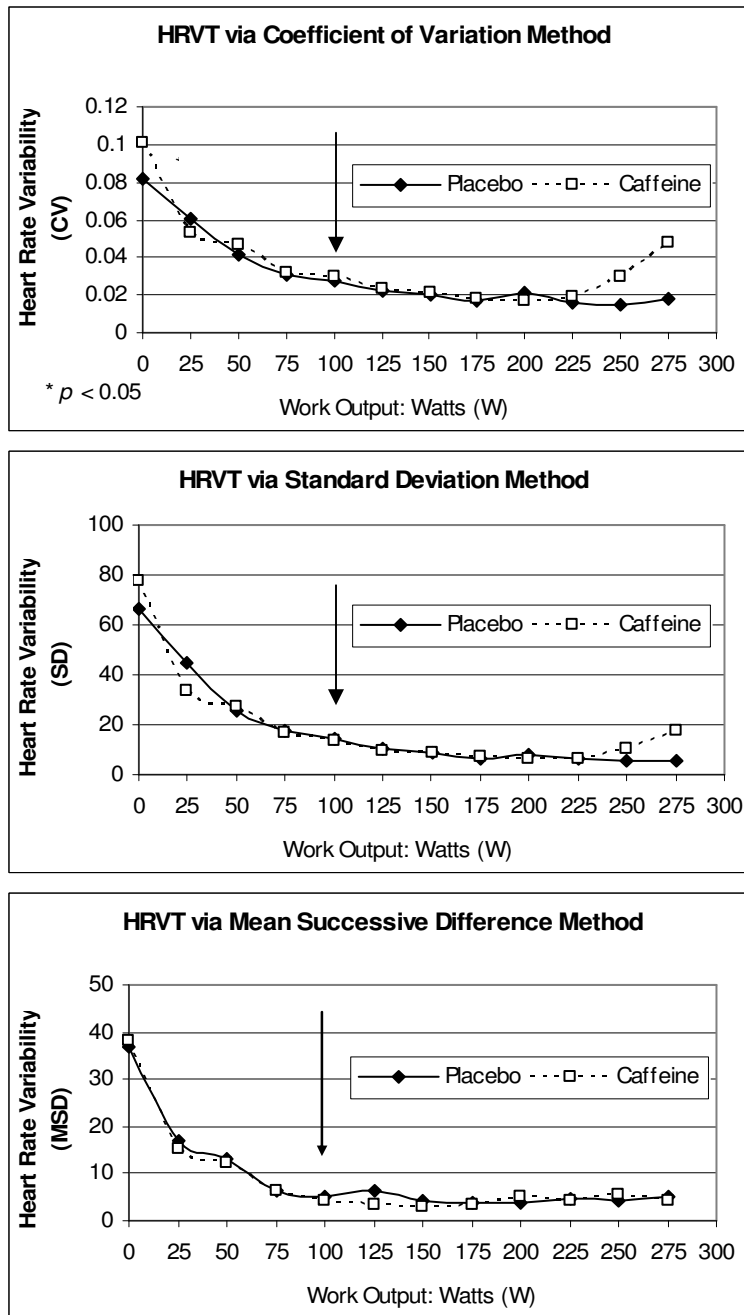


FIGURE 7. Plot of oxygen consumption ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) versus coefficient of variation ($p < 0.05$), standard deviation, and mean successive difference (the mean absolute difference between consecutive RR intervals), respectively (mean \pm SD). Differences are evident at rest, but as exercise intensity increases, the placebo and caffeine values are similar. Arrow and inset values indicate the VO_2 value at which HRVT occurred in placebo and caffeine trials.

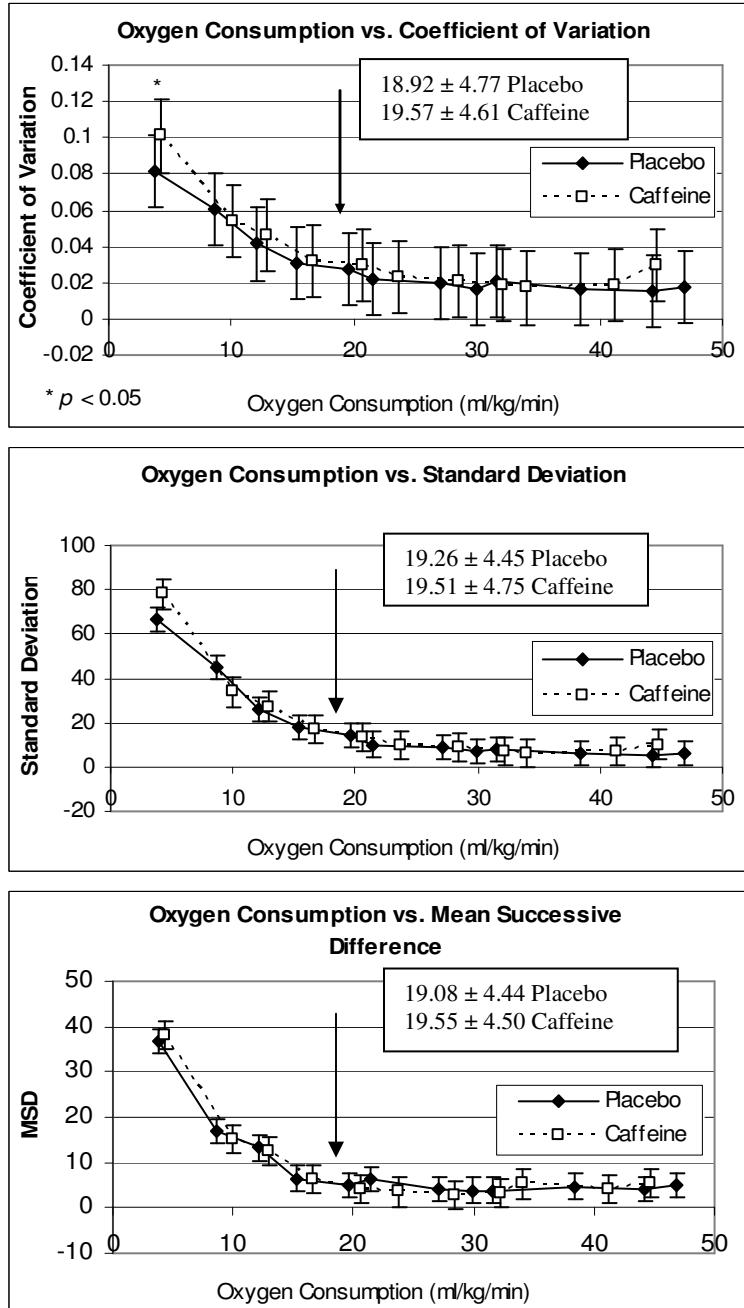


FIGURE 8. Ventilatory Equivalencies. Ventilatory components of V_E/VO_2 and V_E/VCO_2 (L). Each gas exchange data point corresponds to a 20 s interval. X-axis: time (minutes). Y-axis: ventilatory equivalents (V_E/VO_2 and V_E/VCO_2).

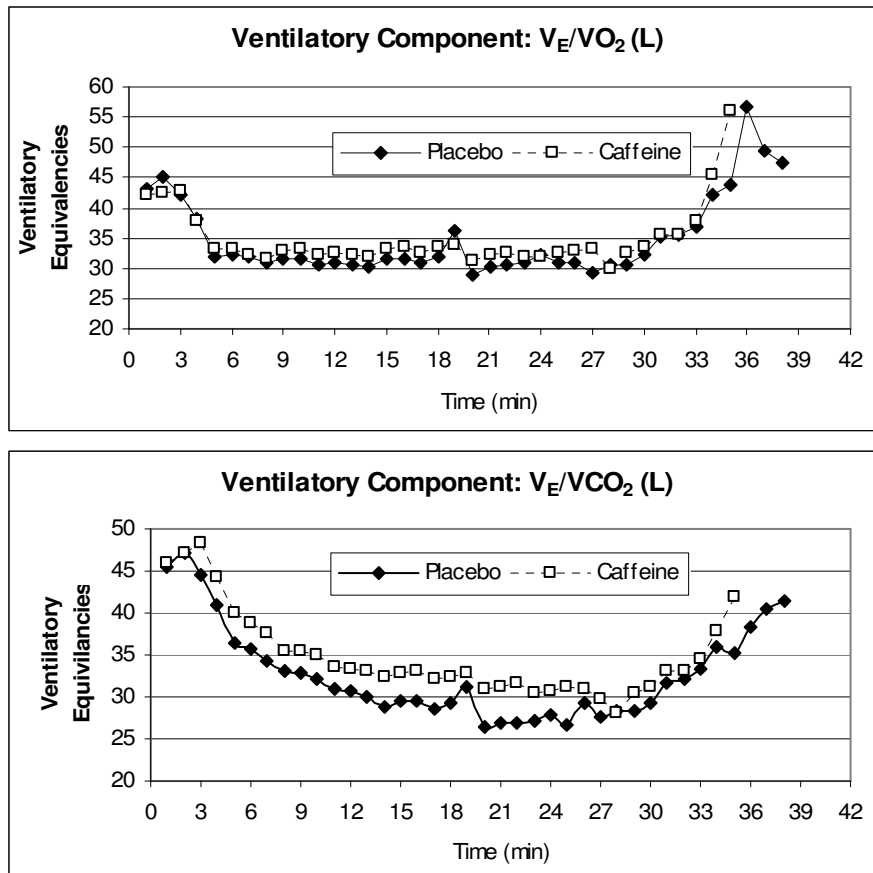
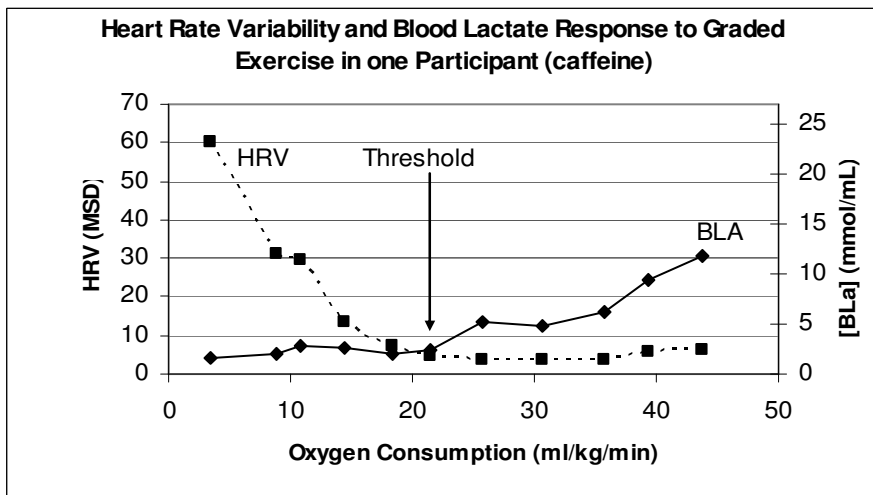


FIGURE 9. Heart Rate Variability and blood lactate response to graded exercise in one participant (caffeine). Visual detection of HRVT (HRV deflection point indicated by arrow) using MSD, coupled with the LT detection as seen by a marked increase in BLA concentration.



Study 3

The results of the third study reveal the LT, VT and HRV response to progressive exercise in obese African American breast cancer survivors. The mean resting VO_2 value was $2.23 \pm 0.58 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. This value may be considered low for normal healthy individuals, however when body composition is taken into consideration (42.02 ± 4.17 body fat percentage), the result is better understood. Although this study did not employ a maximal test, the mean ending VO_2 value was $10.21 \pm 2.22 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Mean resting BLa value was $2.75 \pm 0.96 \text{ mmol}\cdot\text{L}^{-1}$ while mean ending BLa value was $5.65 \pm 1.60 \text{ mmol}\cdot\text{L}^{-1}$. The rise in BLa values can be seen in Figure 10. The mean value for maximal respiratory exchange ratio observed in the cycle ergometry test reached 1.11 ± 0.07 , suggesting that despite the test's submaximal design, high efforts were obtained. Exercise test times ranged from 6 to 17 minutes, with a mean duration of 11.45 ± 1.99 minutes. Only three participants completed the 100W stage (15 minutes). The VT determined by the ventilatory equivalent method can be seen in Figure 11.

Time domain indices plotted against time and oxygen consumption determined the HRVT deflection point as seen in Figures 12 and 13, respectively. Mean values of HRVT indices of SD, CV and MSD were not significantly different from one another (F ($df = 2, 156$) = 0.05, $p = 0.38$). These means are shown in Table 4. Mean values for VT, LT, and HRVT were not significantly different from one another (F ($df = 2, 156$) = 0.24, $p = 0.32$). These values are displayed in Table 5. The RR interval data were used to determine HRVT during graded exercise testing by comparing VO_2 ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) to the respective indices of HRV (Figure 13). A typical example of this threshold is displayed in (Figure 14). Upon initiation of exercise all HRV index values rapidly declined, reaching a

mean deflection point at $5.69 \pm 1.12 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, and remained uniformly low throughout the remainder of the test (Figure 12). These mean HRV indices had a good correlation with the VT ($r = 0.95$) and LT ($r = 0.83$) respectively, and were determined to be the HRVT (Table 5).

The plots in the left panel of Figure 15 graphically display the respective correlations between VT, LT, and HRVT. The Bland-Altman plots are seen in the right panel where dark lines are provided at ± 3 SD on each graph. The mean of VO_2^{vt} and VO_2^{lt} for each participant was plotted against the difference between the VO_2^{vt} and VO_2^{lt} in the Bland-Altman plot of Figure 15 (top right), which illustrates good agreement. Likewise, the mean of $\text{VO}_2^{\text{hrvt}}$ and VO_2^{lt} for each participant was plotted against the difference between the $\text{VO}_2^{\text{hrvt}}$ and VO_2^{lt} in the Bland-Altman plot of Figure 15 (middle right), which also illustrates good agreement. Finally, the mean of $\text{VO}_2^{\text{hrvt}}$ and VO_2^{vt} for each participant was plotted against the difference between the $\text{VO}_2^{\text{hrvt}}$ and VO_2^{vt} in the Bland-Altman plot of Figure 15 (bottom right), which illustrates good agreement as well.

When the respective HRV indices were compared to time, agreement between all three HRV indices occurred near 200 seconds. This time equates with the 25W stage of the exercise test, and little further decline in HRV took place thereafter (Figure 12).

TABLE 4. Non-significant differences ($p > 0.05$) between three mean measurements of HRV at threshold (mean \pm SD).

	HRVT
HRV: Standard Deviation	5.73 ± 1.12
HRV: Mean Successive Difference	5.66 ± 1.13
HRV: Coefficient of Variation	5.68 ± 1.11

TABLE 5. Submaximal responses to exercise test. Non-significant differences ($p > 0.05$) between mean values for respective thresholds (mean \pm SD).

VT ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	5.80 ± 1.16
LT (mmol/L)	5.89 ± 1.12
HRVT	5.69 ± 1.12

FIGURE 10. Plot of oxygen consumption ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) versus blood lactate.

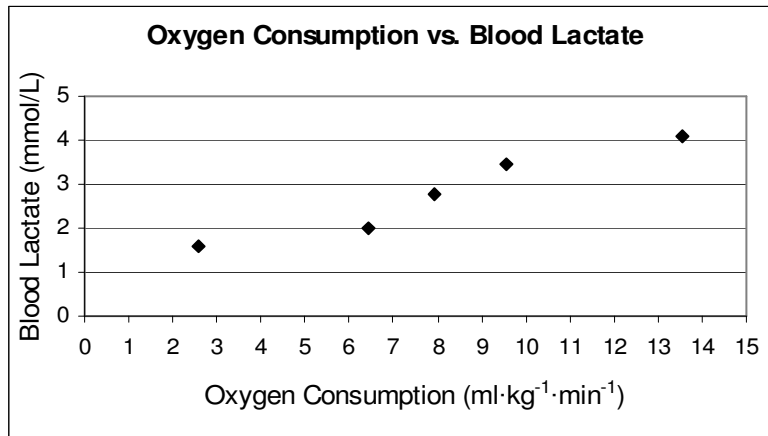


FIGURE 11. Ventilatory Equivalencies. Ventilatory components of V_E/V_{O_2} and V_E/V_{CO_2} (L). Each gas exchange data point corresponds to a 20 s interval. X-axis: time (seconds). Y-axis: ventilatory equivalents (V_E/V_{O_2} and V_E/V_{CO_2}).

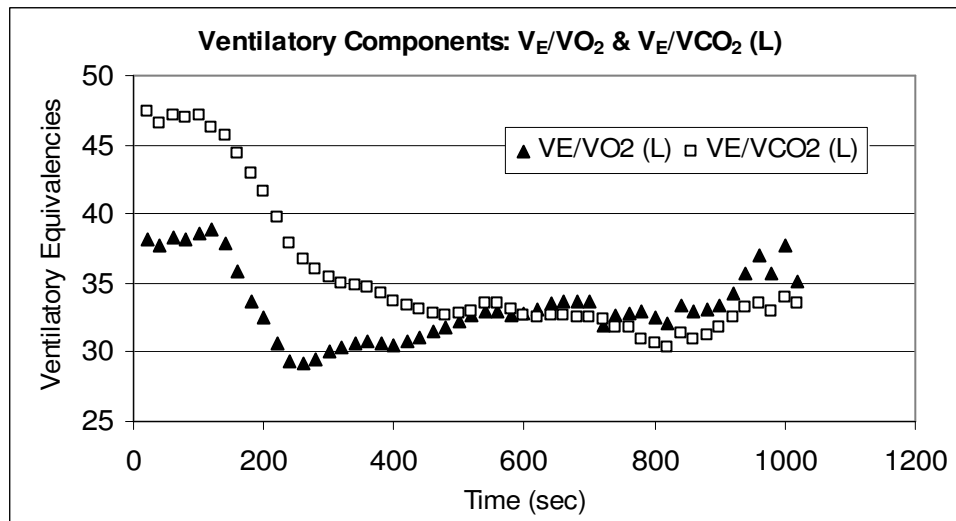


FIGURE 12. Heart Rate Variability Threshold. HRVT is defined via three different measurements (SD, CV, MSD) versus time (seconds). When the respective HRV indices (means \pm SD) are compared to time, the agreement between all three HRV indices occurs during the 25W stage of exercise. Arrow indicates the point at which vagal withdrawal took place and where little further decline in HRV occurred thereafter.

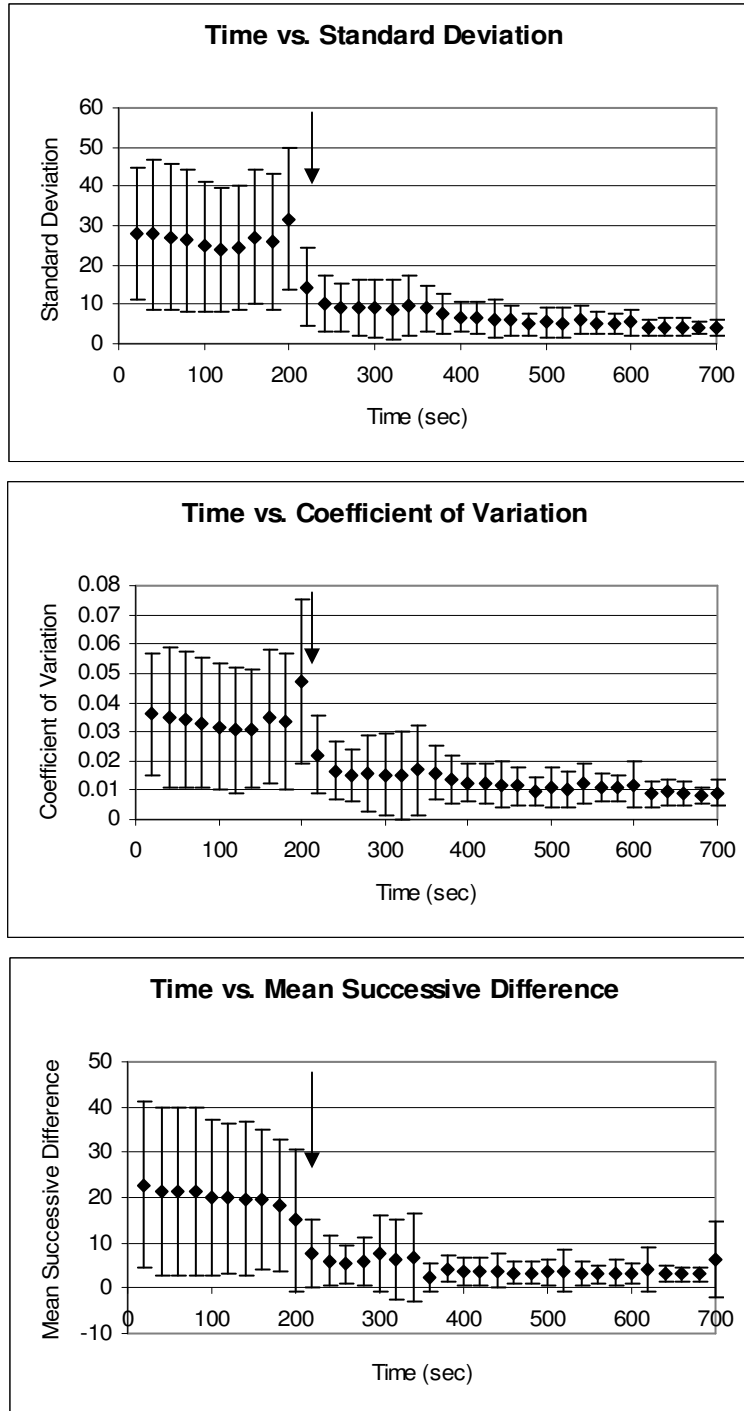


FIGURE 13. Plot of oxygen consumption ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) versus standard deviation, coefficient of variation, and mean successive difference (the mean absolute difference between consecutive RR intervals), respectively. Arrow indicates the VO_2 value at which mean VT occurred ($5.80 \pm 1.16 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$).

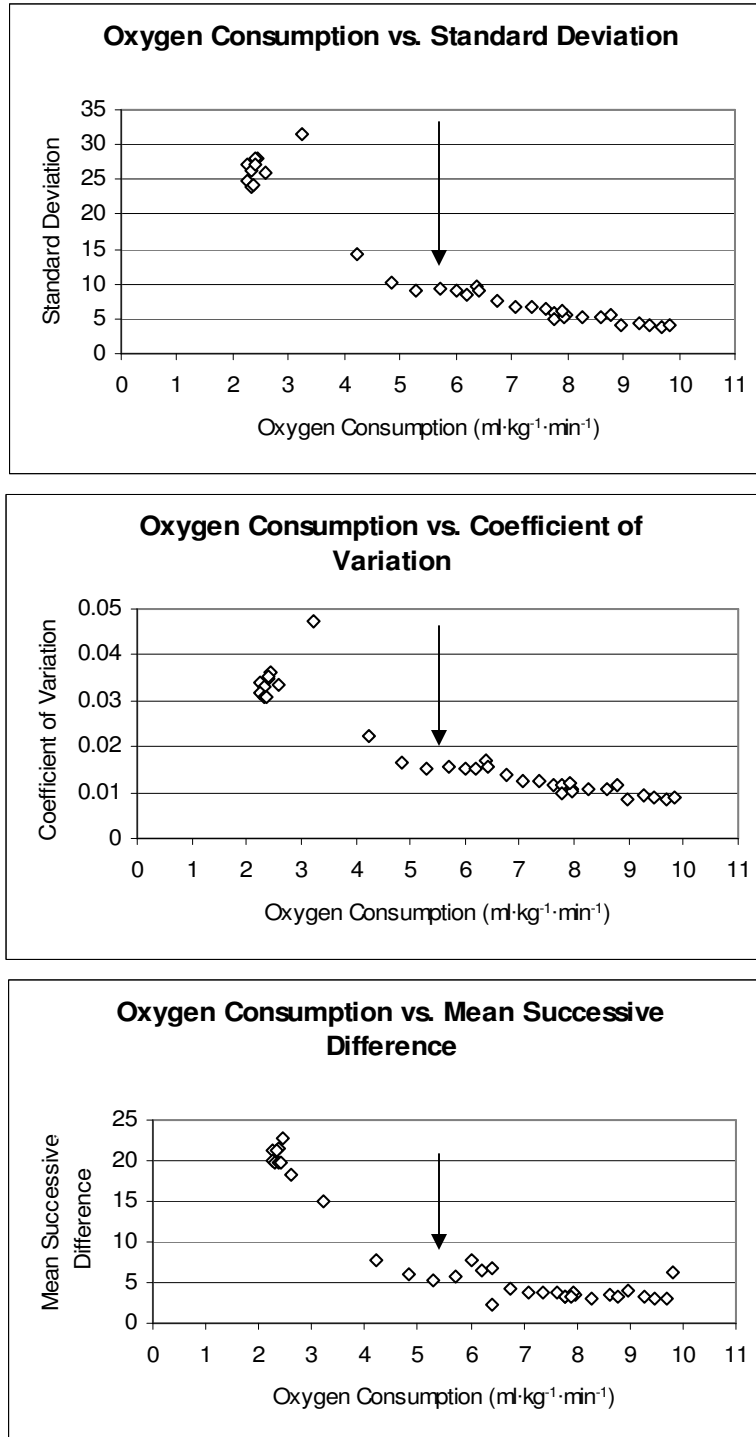


FIGURE 14. Example of heart rate variability response to graded exercise in one participant. Visual detection of HRVT (HRV deflection point indicated by arrow) versus oxygen consumption ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$).

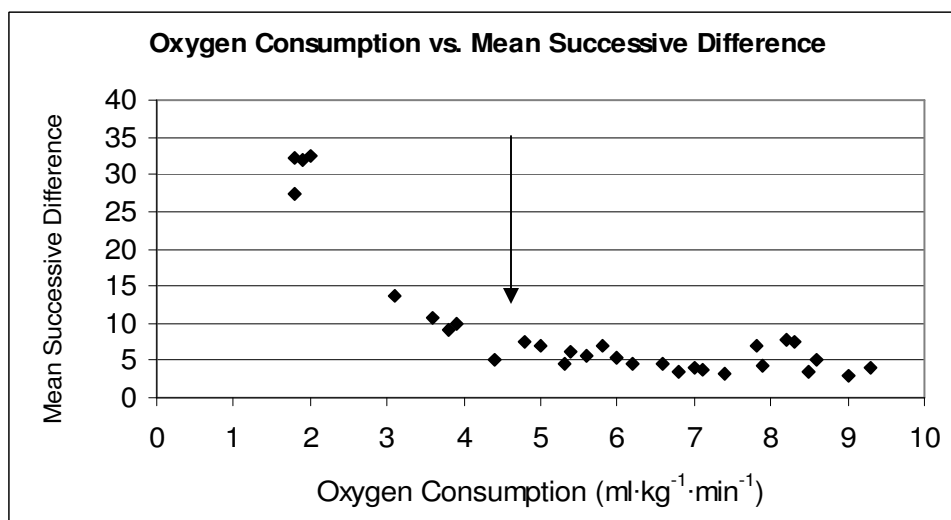
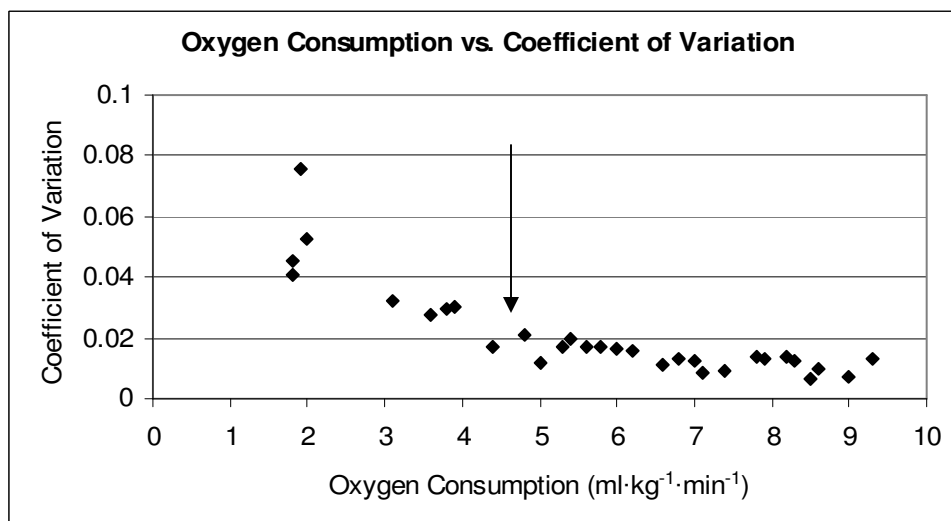
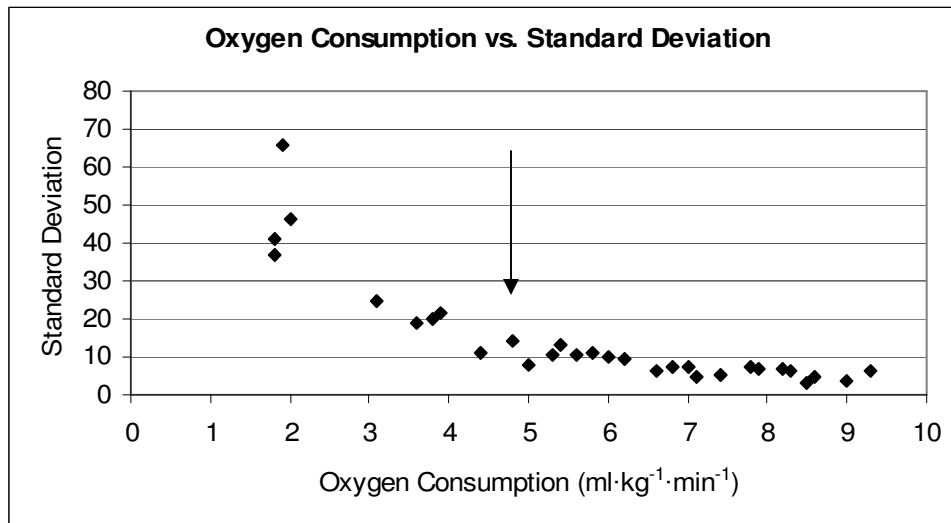
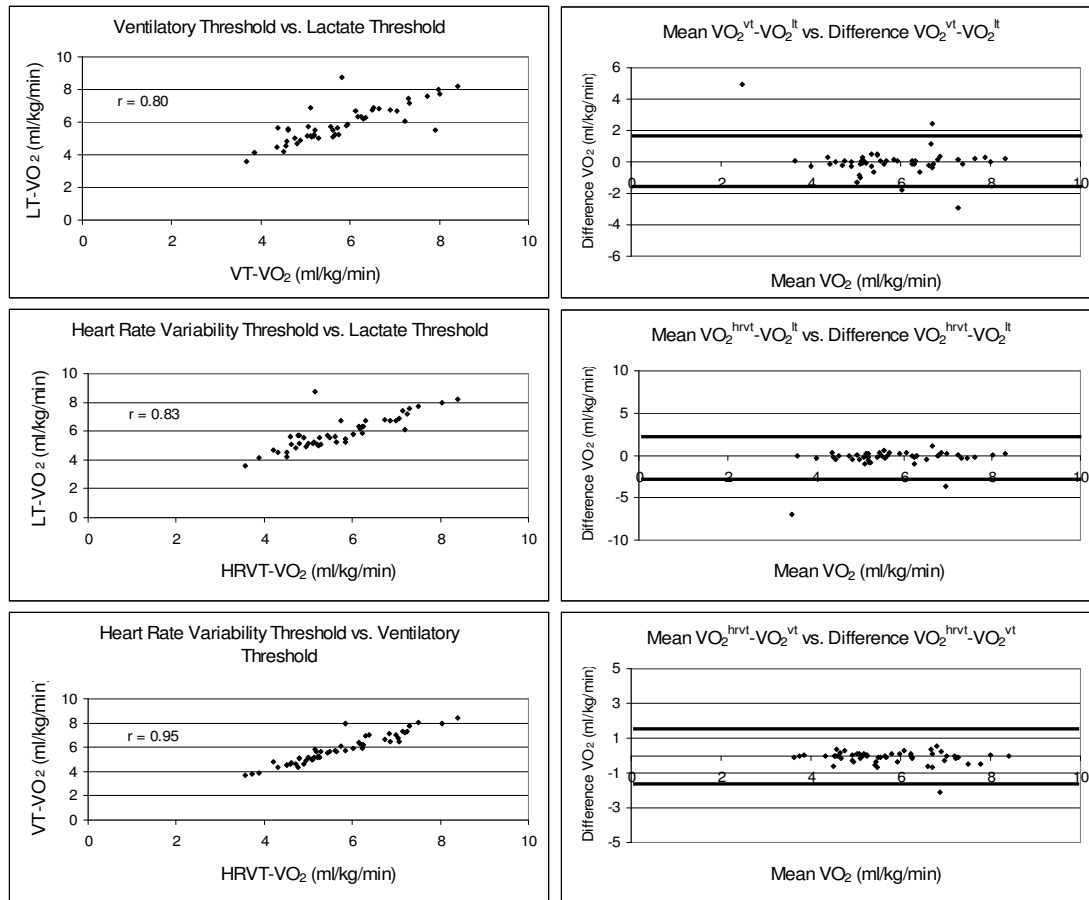


FIGURE 15. Validity testing of VO_2^{vt} , VO_2^{lt} , and VO_2^{hrvt} . The *left panel graphs* show the relationship of VO_2^{vt} vs. VO_2^{lt} , VO_2^{hrvt} vs. VO_2^{lt} , and VO_2^{hrvt} vs. VO_2^{vt} with a line of best fit and correlation coefficient (r) shown on each graph. The *right panel graphs* are Bland-Altman plots. These graphs plot the respective difference between VO_2^{vt} , VO_2^{lt} and VO_2^{hrvt} (y-axis) for each participant against the means of VO_2^{vt} and VO_2^{lt} , VO_2^{hrvt} and VO_2^{lt} , and VO_2^{hrvt} and VO_2^{vt} . The *dark lines* in each Bland-Altman plot represent ± 3 SD, which displays a strong agreement between the various methods among the breast cancer survivors.



CHAPTER 5 DISCUSSION

Study 1

The discussion of the first study in determining if changes in HRV during incremental exercise can be used to estimate LT and VT in healthy adults is as follows.

Relationship between HRVT, LT and VT

Few studies have focused on the relationship between HRVT using time domain RR interval analysis, LT and VT determination during an incremental exercise test. The findings of previous research (Berry, Stoneman, Weyrich, & Burney, 1991) also suggest that differences in LT and VT may be the result of sympathetic nervous system stimulation, wherein the LT may occur by activation of muscle glycogenolysis, and the increases in sympathetic-adrenal activity during exercise provoke an increase in catecholamines, which could be responsible for stimulating ventilation. Changes in ventilation, detected by an elevation in VCO_2 , and HR control have been found in relation to the aerobic-anaerobic transition during exercise (Anosov, Patzak, Kononovich, & Persson, 2000). In an examination of the effects of incremental exercise on HRV, a shift in the instantaneous frequency of the high-frequency component of HR occurred during the transition from aerobic to anaerobic work, as detected via VT (Anosov et al., 2000). The transition to anaerobic metabolism was detected via VT in that study. Heart rate variability is mainly vagally mediated (Karemaker & Lie, 2000), and it has been found that HRV decreases during exercise phases when HR increments are determined mainly due to vagal withdrawal (Alonso et al., 1998). Vagal modulation of HR generally disappears at 50-60% of $\text{VO}_{2\text{max}}$ (Tulppo et al., 1998), which is the range in which LT appears (Chwalbinska-Moneta, Robergs, Costill, & Fink, 1989).

Incremental increases in exercise intensity result in higher HR, lower RR intervals, and overall lower HRV (Tulppo et al., 1996) nearing the point of the VT, which may coincide with a reduction of vagal activity to the heart (Warren et al., 1997) as the sympathetic nervous system dominates its influences on HR via the effects of sinoatrial node automaticity. A simultaneous rise in tidal volume and breathing frequency (Clark, Hagerman, & Gefland, 1983; Gaskill et al., 2001) that coordinates with the VT, could further support the result of a mechanical effect of the sinus node (Kohl, Kamkin, Kiseleva, & Streubel, 1992) which induces a rise in high-frequency power that coordinates with the VT (Blain, Meste, & Bermon, 2005; Cottin et al., 2006).

Previous studies (Anosov et al., 2000; Shibata et al., 2002) have established that significant changes in HRV and vagal activity coincide with the regions of LT. The present work showed similar results, using different measures to assess HRVT. This study demonstrates a marked RR interval deflection point in the stage of exercise in which LT took place (determined via BLa levels). The large increase in BLa production may be linked to an increase in sympathetic output, wherein the sympathetic domination of the autonomic nervous system coincides with vagal withdrawal. The RR deflection point was indicated as the region at which HRVT occurred for each participant. When sympathetic nervous system domination occurs, and vagal withdrawal takes place (Rowell, 1993) the RR intervals measured by SD and MSD (Hayano et al., 1991) markedly decrease, coinciding with vagal withdrawal as well as VT and LT.

Shibata et al. (Shibata et al., 2002) examined cardiac vagal activity and its response to exercise intensity changes and found that HRV decreased with increasing work rate, and changed little after reaching individual-specific work rate. Their results

showed that vagal activity disappeared at this point and the HR at this exercise intensity was determined as the vagal activity threshold. Anosov et al. examined the relationship between HRV and VT (termed Anaerobic Threshold in that investigation) using ramp-load experiments for exercise testing. This study showed a strong correlation between the high-frequency component (0.18-0.4 Hz) of HRV and ventilation by detection of VT (Anosov et al., 2000). Both parameters changed in parallel with increasing exercise intensity. The high-frequency component of HRV is known to be synchronous with respiration and has been considered a quantitative evaluation of respiratory sinus arrhythmia, which is mediated solely by the vagus nerve. The low-frequency component (0.04-0.15 Hz) is mediated by both the vagus and cardiac sympathetic nerves, and its activity reflects sympathetic activity with vagal modulation (Kristal-Boneh, Raifel, Froom, & Ribak, 1995). The results of that study showed a change in the high-frequency component in the region of VT (determined via V-slope method) for 91% of the participants. The instantaneous phases and frequencies showed a deflection that was correlated well to VT. Additionally, Blain et al. demonstrated that VT could be assessed by using a time varying analysis of HRV measurements on a graded and maximal cycle ergometry test (Blain, Meste, Bouchard et al., 2005). Their study revealed that thresholds of respiratory sinus arrhythmia correlated well and were not significantly different with VT ($r = 0.99$, $p < 0.001$). The current study suggests that vagal withdrawal may be the corresponding factor that marks the thresholds of lactate, ventilation, and HRV.

Relationship Between VT and LT

There is an established relationship between VT and LT (Aunola & Rusko, 1986; Burke, Thayer, & Belcamino, 1994). Additionally, ventilatory and lactate-derived

thresholds have shown a high and similar reproducibility (Dickhuth et al., 1999), where the two should be considered separate but associated thresholds (Myers & Ashley, 1997). The current study also revealed a strong relationship between LT and VT using the combined method for determination (Gaskill et al., 2001). While agreement is high that LT and VT are closely related, some studies have questioned their equivalence. Chicharro et al. detected VT before LT (Chicharro et al., 1997) (as it was in our study despite a high correlation between them). Chicharro et al. suggested H^+ could be extracted from the muscle cells independently of the lactate transporter, so ventilation can increase disproportionately without a rise in plasma lactate concentrations (Chicharro et al., 1997). The release of H^+ causes an increase in non-metabolic carbon dioxide, derived from the buffering of hydrogen ions. It was proposed by Wasserman et al. that this is the mechanism responsible for eliciting the rise in VT before the rise in LT (Wasserman, Beaver, & Whip, 1986).

The present study showed a small (0.12 L/min), non-significant difference ($p > 0.05$) between means of VT and LT detection, where the physiological difference is probably negligible. VT was detected before LT in most cases because ventilatory parameters were measured every 20 seconds, whereas lactate samples were measured at the end of each 3 minute stage. Therefore, there was a greater opportunity to detect VT before LT. Although VT was detected at a different VO_2 value than LT, both VT and LT occurred at the same stage/workload of exercise.

If LT, VT, and HRVT all provide similar results, as was shown in this study, the addition of HRVT would expand the tools available to trainers, athletes, and clinicians. The use of LT and VT has long been advocated for improving performance (Denis,

Fouquet, Poty, Geysant, & Lacour, 1982), however the measurement of VT is cumbersome and ventilatory gas analysis equipment is expensive. In addition, while relatively inexpensive lactate analyzers are available, finger prick analysis is an invasive procedure, and test strips can become costly. Alternatively, HRVT can be determined using a HR monitor with RR interval capability. The results of the present study are in accordance with those of Cottin et al. in which VT was determined from RR interval data using HRV time-frequency analysis during a cycle ergometer test (Cottin et al., 2006). In that study high-frequency thresholds were not significantly different and well correlated with VT. Cottin et al. also used an RR recording HR monitor in elite level athletes during an incremental running test on a track and showed a strong correlation between ventilatory and high-frequency band thresholds ($r = 0.96, p < 0.001$) (Cottin et al., 2006; Cottin et al., 2007).

This investigation is limited in some areas. While a HRVT and VT appear linked through vagal modulation, it has not been conclusively shown that vagal modulation is the mechanism responsible for VT. The BLa samples served for the determination of LT, and while this study obtained blood samples every 3 minutes, samples taken every minute may have lead to greater accuracy in that measurement. In addition, HRV was analyzed by taking the average values over the course of the final 2 minutes of each stage, as opposed to every minute. In order to obtain stable RR intervals, the 3 minute stage protocol was used in this study, however for a good VT detection, the 1 minute stage protocol is often recommended. While this investigation, as well as others (Blain, Meste, Bouchard et al., 2005; Cottin et al., 2006; Cottin et al., 2007) have clearly shown that changes in HRV can be used to estimate VT and LT, very different analysis techniques

have been used, suggesting this could be a very unique measure, and future studies are needed to determine which techniques work best. In addition, further studies need to be conducted in which HRV is measured during exercise in individuals with a wider range of BMI, ages, fitness levels and co-morbidity risks than what was assessed and measured within the scope of the studies conducted so far.

The ventilatory and lactate responses to exercise are established and important measures in appropriately designing an exercise program for individuals interested in achieving a marked increase in cardiorespiratory fitness. The Null hypothesis for this study was rejected, and the Alternative hypothesis was supported. This suggests that the determination of HRVT is a convenient tool that may be used as a non-invasive surrogate for the detection of VT and LT in normal healthy adults.

Study 2

The discussion of the second study in determining the influence of caffeine on lactate, ventilatory, and heart rate variability thresholds during progressive exercise is as follows. Previous research has addressed the concomitant relationship between LT, VT and HRVT (Gaskill et al., 2001; Wyatt, Godoy, Autrey, McCarthy, & Heimdal, 2005), and although some disagreement does exist (Chicharro et al., 1997), ventilatory and lactate-derived thresholds have shown a high and similar reproducibility (Dickhuth et al., 1999), where the two may be considered separate but associated thresholds (Myers & Ashley, 1997). This study examined the impact of caffeine on measurement indices of HRV during graded maximal exercise performed to volitional fatigue, as well as caffeine's effect on measurements of LT, VT and HRVT. The major findings reveal that at rest, when the parasympathetic nervous system predominates (Karemaker & Lie, 2000)

and the vagus nerve controls HR, caffeine impacts measurements of HRV. However, as exercise intensity gradually increases, caffeine's influence on these parameters is no longer detectable.

Autonomic Nervous System, Vagal Function & Heart Rate Variability

In this study, measurements of resting HR in caffeine and placebo trials did not differ. Some previous studies report the same result (Nishijima et al., 2002), while others observed caffeine induced changes (Dodd et al., 1991). Decreases in HRV measures of parasympathetic nervous system activity suggest that acute ingestion of caffeine, compared to placebo, directly reduces parasympathetic nervous system activity in the short term in humans (Sondermeijer, van Marle, Kamen, & Krum, 2002). The results of this study propose that these differences are evident at rest, however when exercise intensity increases and vagal withdrawal occurs, the sympathetic nervous system has a dominant influence on HR via the effects of sinoatrial node automaticity, and a non-significant difference between caffeine and placebo trial parameters of HRV becomes evident.

Some resting measurements of HRV (SD, MSD) did not differ between placebo and caffeine trials. These findings are consistent with the work of Rauh et al., who indicated that an acute 200 mg dose of caffeine did not influence HRV parameters (Rauh, Burkert, Siepmann, & Mueck-Weymann, 2006). Increases in exercise intensity result in higher HR and lower HRV (Tulppo et al., 1996), which coincide with a reduction of vagal activity to the heart (Chiou & Zipes, 1998). At this point, when the sympathetic nervous system dominates and cardiac vagal control is less effective (Rowell, 1993), caffeine failed to demonstrate a significant effect on measurements of LT, VT or HRV

when compared to placebo measurements ($p > 0.05$). The current results do not support caffeine's influence on measurements of HRV beyond the initial baseline resting phase of an incremental maximal cycle ergometry test or on physiologic thresholds such as LT, VT or HRVT.

Heart Rate Variability Threshold

HRV is mainly vagally mediated (Karemaker & Lie, 2000), and it has been found that HRV decreases during exercise phases when HR increments are determined mainly due to vagal withdrawal (Alonso et al., 1998). RR intervals of heartbeats have been measured in conjunction with caffeine intake, and results suggest an increase in vagal autonomic nerve activity (Hibino et al., 1997). Vagal modulation of HR generally disappears at 50-60% of VO_{2max} (Tulppo et al., 1998), which is also near the point at which the onset of BL_a accumulation occurs (Chwalbinska-Moneta et al., 1989), causing an increase in ventilation and carbondioxide excretion. An association between VT and withdrawal of vagal activity has previously been observed (Tulppo et al., 1996). This may suggest a link between autonomic nervous system status and VT and presents an interesting concept as HRV is under the same type of control system.

The initial study in this dissertation detected a HRV "threshold" when examining changes in HRV during progressive exercise, wherein it was suggested the HRVT coincides with LT and VT during graded exercise. In the current study, caffeine affected resting measurements of HRV, yet failed to display the same impact once the exercise protocol began (Figures 6, 7). This study is consistent with the initial study of this dissertation, indicating a strong correlation between HRVT and LT ($r = 0.99$), and between HRVT and VT ($r = 0.99$). The current HRV data further suggest that regardless

of the effects of caffeine, a coinciding HRVT does exist where the RR deflection point was indicated as the region at which HRVT occurred (Figures 6, 7). As exercise intensity increases and the SNS dominates, vagal withdrawal occurs (Rowell, 1993) and the RR intervals measured by CV, SD and MSD (Hayano et al., 1991) markedly decrease. This HRVT coincides with vagal withdrawal as well as LT and VT (Table 3) despite caffeine ingestion.

Lactate and Ventilatory Thresholds

The first study in this dissertation has suggested that significant changes in HRV and vagal activity may coincide with the regions of LT and VT. The current study demonstrates a marked RR interval deflection point in the stage of exercise in which LT took place (determined via BLa levels) in both placebo and caffeine trials. Caffeine significantly increased BLa values at rest (Table 3, Figure 4), but had no significant impact throughout the exercise portion of the test. This outcome may motivate a larger sample size be used in future studies, but nevertheless, the results are consistent with Powers et al. who revealed that rate of BLa accumulation was not significantly different between caffeine and placebo trials (Powers et al., 1983). The current results indicate no difference between placebo and caffeine trial LT (Table 3), which is consistent with the findings of others (Dodd et al., 1991).

The current data shows that caffeine significantly increased V_E volumes at rest, indicating caffeine's respirogenic effect. This response is in agreement with Spriet et al. where significant increases in V_E volumes were evident during exercise for the majority of an endurance performance test after a $9 \text{ mg}\cdot\text{kg}^{-1}$ dose of caffeine (Spriet et al., 1992). Similar to the current study, Dodd et al. also reported a significant increase in resting V_E

in caffeine naïve participants, however did not find significant differences in exercise V_E volumes. Dodd et al. further noted that resting V_E was not elevated in the caffeine habituated participants of their study, suggesting the central ventilatory stimulatory effect of caffeine is greater in caffeine naïve participants at rest (Dodd et al., 1991).

Caffeine ingestion significantly increased VO_2 at rest, but had non-significant effects on exercise VO_2 values. These findings are concurrent with other studies (Dodd et al., 1991). In addition, VO_{2max} remained unchanged between placebo and caffeine trials, a finding that is also supported by the work of others (Dodd et al., 1991; Powers et al., 1983). Engels et al. demonstrated that pretrial caffeine ($5 \text{ mg}\cdot\text{kg}^{-1}$) significantly increased VO_2 ($p < 0.05$), while other parameters such as cardiac output, HR, stroke volume, and systemic vascular resistance were not significantly different between caffeine and placebo trials (Engels et al., 1999). Likewise, the present study indicates a non-significant difference between placebo and caffeine trial VT.

Time varying analysis of HRV measurements during cycle ergometry testing has demonstrated that thresholds of respiratory sinus arrhythmia are significant and correlated well with VT ($r = 0.99$, $p < 0.001$) (Blain, Meste, Bouchard et al., 2005). Similarly, others have demonstrated that VT can be determined from RR interval data using HRV time-frequency analysis (Cottin et al., 2006). The initial study in this dissertation has addressed this relationship and has suggested that vagal withdrawal may be the corresponding factor that marks the thresholds of lactate, ventilation, and HRV. Importantly, the present data indicate that ingestion of a physiological dose of caffeine has no significant effect on these physiological thresholds.

This investigation does have limitations. Analysis of HRV utilized average values from the last 2 minute of each 3 minute stage of exercise. The 3 minute stage protocol was used in this study in an effort to acquire stable RR interval measurements, however for a good VT detection; the 1 minute stage protocol is often suggested. Also, BLA samples were taken at the end of each 3 minute stage, where samples obtained every minute may have lead to greater accuracy in determining LT.

The initial study in this dissertation describes a relationship between LT and VT, and suggests that both coincide with vagal withdrawal (noted by decreased parasympathetic nervous system activity and increased sympathetic nervous system activity) during progressive exercise. The vagal withdrawal response was also observed in measurements of HRV that are associated with parasympathetic nervous system and sympathetic nervous system activity. A relationship between HRVT, LT and VT was suggested. The current study demonstrates that ingestion of $5 \text{ mg}\cdot\text{kg}^{-1}$ caffeine does exert a significant respirogenic effect and affects some resting HRV measurements, but does not alter the LT, VT or HRVT during progressive exercise. Thus, the relationship between the lactate, ventilatory and heart rate variability thresholds appears to exist, even when challenged by a physiological dose of caffeine. The Null hypothesis for this study was therefore rejected, and the Alternative hypothesis was supported.

Study 3

The discussion of the third study, which measured the VT, LT and HRV response to progressive exercise in obese African American breast cancer survivors, is as follows. Some early literature questioned the association between VT and LT (Brooks, 1985; Neary, MacDougall, Bachus, & Wenger, 1985), but more recently an increasing number

of authors have demonstrated a notable relationship between the two thresholds in various groups (Belli et al., 2007; Gaskill et al., 2001; Wyatt, 1999; Wyatt et al., 2005). Furthermore, Wyatt et al. analyzed HR threshold and its relationship with VT and LT in a cycle ergometry test, and indicated no statistical variance between the three thresholds (Wyatt et al., 2005). The current study also utilizes a cycle ergometry test, but furthers the autonomic aspect of the research by analyzing HRV and a relationship between VT, LT and HRVT has been put forth. Also similar to the current study, the work of Belli et al. established a relationship between VT and LT in women with type 2 diabetes mellitus (Belli et al., 2007), indicating no significant differences ($p > 0.05$) and a good correlation between the thresholds. To our knowledge, this is the first study to look at this relationship, and additionally the relationship of HRV, in obese African American breast cancer survivors.

The vagus nerve controls HR while the parasympathetic nervous system predominates at rest (Karemaker & Lie, 2000). With an increase in physical activity the sympathetic nervous system begins its principal influence over the heart, resulting in higher HR and lower HRV (Tulppo et al., 1996). This parasympathetic to sympathetic switch occurs at a very similar point as the reduction in vagal activity to the heart (Chiou & Zipes, 1998). As demonstrated in the initial study of this dissertation, changes in HRV during progressive exercise have been shown to exhibit a threshold response, which corresponds to the VT in young, healthy participants. Similarly, the current study displays a HRVT that correlates well with the VT ($r = 0.95$).

A possible cause for lower HRV that is manifested in disease is an increased dominance of the sympathetic nervous system and its influences on HR via the effects on

sinoatrial node automaticity. This sympathetic dominance of heartbeat may coincide with vagal withdrawal, resulting in a higher HR and lower HRV. Various physiological conditions, especially the presence of disease, obesity, fitness level, and physical activity influence both the parasympathetic nervous system and sympathetic nervous system affecting HR. It is mainly the vagus nerve which controls HRV (Karemaker & Lie, 2000), and when sympathetic dominance of heartbeat occurs, the vagus nerve withdraws its dominion of HR and the sinoatrial node and baroreceptors take control. It has been suggested vagal withdrawal leads to a decrease in HRV (Alonso et al., 1998). In addition, at 50-60% of VO_{2max} , vagal modulation of HR generally disappears (Tulppo et al., 1998) and a corresponding accumulation of BLA occurs, which can cause an increase in ventilation and carbon dioxide excretion. It has been proposed the mechanism responsible for VT is the vagal modulation of breathing, replaced by sympathetic control (Tulppo et al., 1996).

The problem of obesity and its carryover to multiple comorbidities including insulin resistance and breast cancer prognosis is of immense concern to the African American breast cancer survivor group (Chlebowski et al., 2002) where it is known that proportionally, a greater number of African Americans, as compared to European-Americans, have high insulin levels, are diabetic, and are obese (Davidson, 2001; Mokdad et al., 1999; Okosun, 2001). Post-diagnosis breast cancer, African American women have been reported to gain twice as much body weight as their European-American counterparts (Rock et al., 1999). With a proper exercise prescription specific to obese African American female breast cancer survivors, a change in the risk of recurrence may transpire.

Tamoxifen is an antiestrogen that has been considered the gold standard in adjuvant hormone therapy for the treatment of breast cancer in postmenopausal women. Taxanes (e.g., paclitaxel) are another important group of medications in the adjuvant treatment of breast cancer, and in one study, impairment of autonomic modulation of HR was reported after paclitaxel therapy based on two, twenty-four-hour ambulatory electrocardiogram recordings (Ekholm et al., 2000). That study noted however, that it was not clear if the observed changes were permanent or whether autonomic cardiac function returns to normal after such an intervention. In the current study however, paclitaxel was not a medication that participants were prescribed. Study participants either completed adjuvant drug therapy, or tamoxifen was the most common medication. To our knowledge, there are no reports on the relationship between tamoxifen and HRV measurements.

Furthermore, clinical exercise prescription based on a HRVT may suggest that walking is the most appropriate form of exercise intervention as many participants reached their LT, VT and HRVT before completing the first stage of exercise at 25W. Because of the expense, lack of availability to the general public, and difficulties associated with metabolic testing, an easy to use heart rate based model (derived from HRV and sympathetic nervous system measurements) would be ideal in assisting this group to greater physical activity and leading a healthier lifestyle.

This study can be improved in some areas. For a good detection of VT, many studies employ 1 minute stages of exercise. The 3 minute stage in the current study however, served a dual purpose: the time interval allowed for stabilization of HRV measures, and also provided this sample enough time to complete a meaningful test. With

a low capacity for aerobic exercise, had 1 minute stages been employed, the overwhelming majority of this sample would have completed the exercise portion of the testing procedure within 3 minute (or 75W – the workload at which most participants met the established criterion for ending the test). Shorter stages (1 minute) would have drastically limited data collection for metabolic, BLa and HRV measurements.

Results suggest that changes in HRV can be used to determine a HRVT, which clearly existed and correlated well with other established physiological thresholds such as the LT and VT. Therefore, the Null hypothesis for this study was rejected, and the Alternative hypothesis was supported.

This in turn, strongly suggests this sample has an extremely low tolerance for exercise. Physical activity is an effective recommendation for weight loss; however, because of the low capacity for aerobic exercise in this sample, initial recommendations for increasing physical activity should consider limiting activities that exceed the intensity of brisk walking. The findings indicate this group must carefully determine which established exercise guidelines to follow. In addition, the African American breast cancer survivor database includes individuals taking a range of medications, which influence sympathetic/vagal tone. Therefore, future analyses will include comparison of medications known to influence sympathetic tone.

Final Conclusion

The work of this dissertation suggests that changes in heart rate variability can be used to identify the existence of a heart rate variability threshold. Furthermore, the HRVT can be used to identify important physiological markers such as the ventilatory and lactate thresholds. The three studies of this dissertation have demonstrated that a

HRVT exists among samples of healthy young adults; healthy young adults challenged by a physiological dose of caffeine; and obese breast cancer survivors with a very low capacity for exercise.

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ABSTRACT**HEART RATE VARIABILITY AS A NON-INVASIVE BIOMARKER OF
SYMPATHO-VAGAL INTERACTION AND DETERMINANT OF
PHYSIOLOGIC THRESHOLDS**

by

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August 2008

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The objective of this dissertation is to determine if a heart rate variability threshold exists. If so, can this new, non-invasive measurement be used to identify other important physiological thresholds such as the ventilatory and lactate thresholds, and will this measurement produce similar results under different circumstances? Metabolic studies were performed in three distinct samples: normal, healthy participants; healthy participants who were given a physiological dose of caffeine ($5 \text{ mg}\cdot\text{kg}^{-1}$ body weight); and obese breast cancer survivors, stage I, II, or IIIA cancer, free of recurrence; each under controlled laboratory conditions. Voluntary adults were subjected to a graded, maximal or submaximal cycle ergometry test consisting of 3 minute stages progressing at 25W increments. Blood lactate, heart rate, RR interval, and respiratory gas exchange data were obtained at baseline and throughout each test. The caffeine study used a randomized placebo controlled, double-blind study design, where volunteers performed two graded maximal cycle ergometry tests with or without caffeine ($5 \text{ mg}\cdot\text{kg}^{-1}$). The results suggest a

heart rate variability threshold does exist, and coincides with lactate threshold and ventilatory threshold during graded exercise.

AUTOBIOGRAPHICAL STATEMENT

Gregory Karapetian earned a B.S. in Kinesiology (*cum laude*) at Michigan State University, a M.S. in Basic Medical Science at the Wayne State University School of Medicine, and will complete his Ph.D. (*cum laude*) this summer from the Graduate School at Wayne State University in Evaluation & Research with concentrations in microbiology and exercise physiology.

A former Biomedical Research Fellowship recipient in the Department of Gastroenterology at the John D. Dingell VA Medical Center, Gregory has also worked in the Immunology and Microbiology Department at the Wayne State University School of Medicine, and was a Graduate Research Assistant in the Department of Kinesiology and Health Sciences where he worked alongside the DMC Department of Internal Medicine at the Center for Urban and African American Health, an NIH funded program studying obesity and lifestyle factors - including diet, physical activity, obesity-related cardiovascular disease, and cancer. Gregory took part in the Junior Investigator Research Lecture Series at the National Institute of Health in Bethesda, MD and has made numerous scientific poster presentations at both regional and national conferences.

While an undergraduate, Gregory was a member of the Michigan State University varsity swim team, was named on the Dean's list at Michigan State University for five semesters, and was the recipient of the Lawrence Sierra All-University Award in recognition for outstanding academic achievement. He has been the recipient of several academic excellence scholarships from the local and national Armenian community. Gregory and his lovely wife Nayiri make their home in Royal Oak, MI.