EFFECT OF ISOMETRIC TRAINING ON RESTING ARTERIAL PRESSURE IN HYPERTENSIVES

EFFECTS OF ISOMETRIC HANDGRIP TRAINING ON RESTING ARTERIAL PRESSURE AND HEART RATE VARIABILITY IN NEWLY DIAGNOSED HYPERTENSIVES

By

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ABSTRACT

Hypertension is a modifiable risk factor for cardiovascular disease. The current treatment options are drug therapy and lifestyle modifications. A promising lifestyle modification therapy for the management of hypertension is isometric exercise, as several studies have demonstrated that isometric handgrip (IHG) training reduces resting arterial blood pressure (ABP) (Peters et al., 2006; Taylor et al., 2003; Wiley et al., 1992). The purpose of the present investigation was two-fold: 1) to examine the effectiveness of IHG training in reducing resting ABP in newly diagnosed hypertensive patients, in comparison to matched controls receiving advice from a physician about lifestyle modifications; and 2) to examine markers of autonomic function, specifically, heart rate variability (HRV) to determine if changes in the autonomic nervous system (ANS) existed between the two groups of hypertensive adults.

Resting blood pressure and heart rate were assessed with an automated acquisition system before, during and after the 6-week intervention period. Also, power spectral analysis of HRV was used to assess changes in modulation of the ANS. Participants in both groups (n=14) were given lifestyle modification recommendations regarding diet, exercise and stress reduction, while participants in the training group (n=8) also completed a bilateral IHG training protocol 3 times/week at 30% maximum voluntary contraction (MVC).

Our results demonstrate that contrary to our hypothesis, isometric exercise in combination with lifestyle modification recommendations did not result in a reduction of resting ABP or change indices of HRV. Possible explanations for these results are that

unlike previous IHG training, the present study was the first to use home-based training and the small sample size of this investigation would limit our ability to identify alterations in resting ABP or HRV.

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ABP	arterial blood pressure
Ach	acetylcholine
ACE	angiotensin-converting enzyme
ANS	autonomic nervous system
AR	autoregressive modelling
BA	brachial artery
BMI	body mass index
BPV	blood pressure variability
CO	cardiac output
CVD	cardiovascular disease
DBP	diastolic blood pressure
ECG	electrocardiogram
EPI	epinephrine
FFT	fast fourier transform
FMD	flow mediated dilation
GSH	whole blood glutathione
GSSG	oxidized glutathione
HF	high frequency
HRV	heart rate variability
IHG	isometric handgrip
LF	low frequency
LTPAQ	leisure time physical activity questionnaire
MABP	mean arterial blood pressure
mmHg	millimetres of mercury
MSNA	muscle sympathetic nerve activity
MVC	maximum voluntary contraction
NE	norepinephrine
NN	normal-to-normal
NN50	number of interval differences of successive NN intervals greater than 50 ms
NSAIDs	nonsteroidal anti-inflammatory drugs
pNN50	proportion derived by dividing NN50 by the total number of NN intervals
PNS	parasympathetic nervous system
PSA	power spectral analysis
PSD	power spectral density
rMSSD	square root of the mean squared difference of successive NN intervals
RAAS	renin-angiotensin-aldosterone system
ROS	reactive oxygen species
RSA	respiratory sinus arrhythmia
SA	sinoatrial
SBP	systolic blood pressure
SDANN	standard deviation of average NN interval
SDNN	standard deviation of the NN interval
SNS	sympathetic nervous system
TPR	total peripheral resistance
VLF	very low frequency

1.0 REVIEW OF LITERATURE

1.1 Introduction

The magnitude of pressure in the arterial system is of much interest in clinical medicine. The chronic elevation of ABP, also known as hypertension, is a modifiable risk factor for cardiovascular disease (CVD). Hypertension is also associated with an increased incidence of stroke, heart failure, peripheral arterial disease and renal insufficiency (Pescatello et al., 2004).

The prevalence of hypertension worldwide may be as many as 1 billion individuals, leading to 7.1 million deaths per year (World Health Report, 2002). As of 2001, over three million Canadians were diagnosed with hypertension (Statistics Canada, 2005), which is a significant number, considering only one-third of hypertensives are diagnosed (Joint National Committee, 1997). Of those who are diagnosed, one half do not have their blood pressure at recommended values (Joint National Committee, 1997).

CVD, renal disease and stroke are all conditions that could be prevented or diminished if the age related increase in resting ABP was appropriately controlled (Joint National Committee, 2003). Lifestyle modifications and drug therapy are the treatments prescribed for hypertension management. However, antihypertensive drug therapy is costly to the health care system and often results in undesirable side effects for the patient, such as nausea, headaches and dizziness (Khan, 1999). Consequently, physicians should encourage lifestyle modifications such as regular exercise and nutritional counseling for the treatment and control of hypertension since they have minimal costs and side effects, as well as many secondary benefits.

A number of randomized, controlled studies have demonstrated that chronic aerobic exercise training is associated with decreased resting ABP in hypertensives (Rogers et al., 1996; Tanaka et al., 1997; Urata et al., 1987). Thus, aerobic exercise is often recommended for individuals who have an elevated resting blood pressure. Additionally, recent investigations have identified isometric exercise as a potential therapy for hypertensives. Several studies have shown that isometric training with a handgrip dynamometer is capable of lowering resting ABP (Peters et al., 2006; Ray & Carrasso, 2000; Taylor et al., 2003; Wiley et al., 1992).

Various mechanisms for this reduction in resting ABP with chronic isometric training have been proposed, such as changes in cardiac output (CO), baroreflex sensitivity, hormonal factors and the peripheral vasculature (Peters et al., 2006). A change in the modulation of the ANS may also be associated with the decrease in resting ABP (Taylor et al., 2003). HRV analysis is a non-invasive method of assessing autonomic function after a training regimen (Kamath et al., 1993). This type of analysis can establish if attenuations in sympathetic activity or increases in parasympathetic activity are responsible for the hypotensive effect of IHG training.

1.2 Blood Pressure

1.2.1 Definition

Arterial pressure is composed of two values: systolic blood pressure (SBP) is the pressure in the arteries during contraction of the ventricles, while diastolic blood pressure (DBP) represents the arterial pressure when the heart is at rest between contractions.

Resting ABP progressively falls as it flows through the systemic circulation. Therefore, it is highest as it leaves the left ventricle and lowest as it flows into the right ventricle (Tortora et al., 2003). The average pressure in the arteries is defined as the mean arterial blood pressure (MABP). This value takes the time in systole versus diastole into account and is most often used to represent an individual's overall blood pressure.

The magnitude of MABP at any point in time is determined by CO, total peripheral resistance (TPR) and blood volume (Guyton & Hall, 2000). A change in one of these factors must be responsible for any chronic change in resting ABP. CO is the amount of blood pumped by the ventricle per minute and is determined by heart rate and stroke volume. However, aerobic exercise training studies do not demonstrate a significant change in CO following training (Pescatello et al., 2004). Also, changes in blood volume are not likely responsible for adjustments in blood pressure over time. The average adult has 5 liters of blood in their circulation and any modest change is accounted for by homeostatic mechanisms to maintain blood pressure. As a result, only changes in blood volume of 10% or greater will result in alterations in resting ABP (Tortora et al., 2003). Therefore, it is thought that TPR is the main determinant for chronic alterations in blood pressure.

TPR is the opposition of the vessels in the systemic circulation to blood flow. Activity of sympathetic vasomotor nerves, the level of circulating vasoactive hormones and local factors such as metabolites and endothelial factors are all determinants of TPR (Dampney et al., 2002).

1.2.2 Arterial Blood Pressure Regulation

The control systems of CO, blood volume and TPR work together to ensure that ABP is adequate in order to maintain a balance between tissue metabolism and tissue perfusion. Some of these negative feedback systems are capable of rapid adjustments, such as when the body is under the stress of exercise, while others act more slowly to provide long-term regulation (Tortora et al., 2003). Regulatory systems rely on central (neural), peripheral (local) and hormonal control mechanisms, which are all controlled by the cardiovascular center in the medulla oblongata. The cardiovascular center receives input from higher brain regions such as the cerebral cortex, limbic system and hypothalamus as well as from sensory receptors in the periphery (Tortora et al., 2003).

Sympathetic and parasympathetic neurons of the ANS carry the output from the cardiovascular center. Stimulation of the sympathetic nervous system (SNS) causes the release of norepinephrine (NE) and epinephrine (EPI) from sympathetic nerve endings. This results in an increase in rate and contractility of the heart, as well as the contraction of vascular smooth muscle cells, resulting in vasoconstriction (Brooks et al., 1996). Stimulation of the parasympathetic nervous system (PNS) causes the release of acetylcholine (Ach), which results in a lowering of heart rate, vasoconstriction of coronary arteries and vasodilation of areas in the circulatory system (Brooks et al., 1996). Therefore, increased or decreased activation of the SNS and PNS are greatly responsible for maintaining ABP.

1.2.2.1 Neural Regulation

The cardiovascular center, which is also known as the vasomotor center, is largely comprised of nerve cells in the reticular formation of the brain stem (Brooks et al., 1996). The cardiovascular center receives impulses from central command, the hypothalamus, baroreceptors, chemoreceptors and muscle afferents. It then integrates this information in order to influence the rapid control of blood pressure (Brubaker et al., 2002). As previously mentioned, the sympathetic and parasympathetic neurons carry the output from the cardiovascular center.

Baroreceptors are involved in the chronic and acute regulation of blood pressure. They are stretch receptors that are located in the wall of the aorta and carotid arteries and respond to increases and decreases in ABP (Brubaker et al., 2002). Baroreceptors respond to changes in pressure extremely rapidly. For instance, when there is an increase in pressure above the "set point", the baroreceptors are stretched to a greater extent and they send inhibitory signals to the vasomotor center, which causes reflex sympathetic inhibition and parasympathetic activation. This results in a decrease in heart rate and cardiac contractility, as well as vasodilation throughout the peripheral circulatory system, decreasing blood pressure (Brubaker et al., 2002). The opposite occurs when there is a decrease in blood pressure below the set point. In this situation, an increase in sympathetic outflow causes an increase in heart rate and cardiac contractility. TPR also increases as a result of excitatory signals sent to the vasomotor center from the baroreceptors (Brubaker et al., 2002).

Another negative feedback reflex mechanism involved in maintaining optimal MABP is the chemoreceptor reflex. Chemoreceptors are similar to baroreceptors, as they are located in the aorta and carotid arteries. However, instead of responding to stretch, they are sensitive to a lack of oxygen, an increase in carbon dioxide or a decrease in pH (Brubaker et al., 2002). When chemoreceptors are activated by reduced blood flow and oxygen levels and/or a build up of carbon dioxide and hydrogen ions, they send excitatory signals to the vasomotor center to elevate arterial blood pressure through an increase in TPR.

Type III and IV muscle afferents are also involved in blood pressure regulation. They are located in skeletal muscle and are stimulated by mechanical, thermal and chemical stimuli (Brooks, 1996). They are most active during intense exercise when muscle metabolism increases, causing local vasodilation. This vasodilation in muscles would cause ABP to fall if it was not for feedback from muscle afferents, which limits local muscle vasodilation (Brooks, 1996). When muscle afferents are stimulated, they send signals to the cardiovascular center via a negative feedback system. The cardiovascular center then increases blood pressure by increasing heart rate, the strength of cardiac contraction and by vasoconstriction of blood vessels (Brooks, 1996).

1.2.2.2 Hormonal Regulation

Stimulation of the SNS causes secretion of NE at the endings of vasoconstrictor nerves and also influences the adrenal medulla to release EPI and NE (Guyton & Hall, 2000). Both hormones enhance sympathetic stimulation of the heart by increasing its

rate, force and speed of contraction (Brooks et al., 1996). In the periphery, both EPI and NE bind to α-receptors on vascular smooth muscle cells to cause vasoconstriction. EPI also binds to ß- receptors located in skeletal muscle arterioles during exercise to cause vasodilation (Brubaker et al., 2002).

Angiotensin II is another hormone that is capable of exerting an acute effect on arterial blood pressure. The production of this hormone follows the release of renin from the kidney in response to direct adrenergic stimulation, a reduction in renal arterial pressure, or a decrease in the renal tubular sodium reabsorption (Brubaker et al., 2002). Renin cleaves an inactive liver peptide angiotensinogen to produce angiotensin I, which is further catalyzed to angiotensin II by angiotensin-converting enzyme (ACE). In addition to causing vasoconstriction of vascular smooth muscle cells, angiotensin II also stimulates the release of aldosterone, which causes decreased elimination of sodium and water, as well as an increased activation of the SNS (Brubaker et al., 2002). The increase in blood volume caused by the release of angiotensin II results in elevated ABP. The renin-angiotensin-aldosterone system (RAAS) is a long-term regulatory mechanism of arterial blood pressure and extracellular volume, which increases ABP when it is low.

1.2.2.3 Local Regulation

When the supply of oxygen is insufficient to meet the demand in the interstitial space, the arterioles will react by vasodilating to increase blood flow in order to increase the supply of oxygen (Brubaker et al., 2002). Exercise is an example of this local regulation since there is an increased demand for oxygen by the muscles and enhanced

production of carbon dioxide. There are also substances released by the vascular endothelium that are able to cause changes in vascular resistance. Examples are nitric oxide and endothelin. Nitric oxide release is stimulated by shear stress, Ach, bradykinin, histamine, serotonin, and vasopressin to produce vasodilation (Brubaker et al., 2002). Endothelin release is stimulated by hypoxia, damaged endothelium and free radicals to cause vasoconstriction of the arterioles (Brubaker et al., 2002). These factors do not necessarily regulate blood pressure, but they do have an effect on arterial blood pressure due to vasoconstriction or vasodilation of blood vessels. It is believed that local vasodilators are important for lowering TPR and therefore reducing ABP since the SNS predominantly causes vasoconstriction when stimulated, such as during exercise (Brooks et al., 2006).

1.3 Regulation of Heart Rate

1.3.1 Introduction

In addition to cardiac muscle cells, the heart also contains specialized cardiac muscle fibers that instigate and propagate the electrical activity that trigger contractions of the heart. These specialized cardiac muscle fibers are known as autorhythmic because they repeatably generate action potentials and thus act as a pacemaker of the heart (Tortora et al., 2003). These autorhythmic fibers also act as a conduction system as they provide a path through the heart for each cycle of cardiac excitation to pass through. The action potentials are generated by the sinoatrial (SA) node, which acts as the pacemaker of the heart and subsequently travel through the conduction system to stimulate atrial and

ventricular contraction. In the absence of any neurohormonal influences, the intrinsic heart rate generated by the SA node would be between 100 and 120 beats per minute (Malik & Camm, 1995). However, the timing and strength of each cardiac contraction is altered by the ANS and by hormones in the blood in order to meet the blood flow demands under various conditions (Tortora et al., 2003).

The control system that regulates heart rate consists of both the central and peripheral nervous system. The cardiovascular center and medulla oblongata in the CNS receive input from higher brain centers such as the limbic system and cerebral cortex and from sensory receptors in the periphery (Task Force, 1996). The sensory receptors that regulate heart rate are the baroreceptors, chemoreceptors and mechanoreceptors, have been discussed previously. Subsequently, the cardiovascular center influences the SA node by increasing or decreasing the frequency of nerve impulses in the sympathetic and parasympathetic branches of the ANS (Tortora et al., 2003). The parasympathetic nerves slow the heart while the sympathetic nerves accelerate it (Malik & Camm, 1995) and the net effect of the two is represented by the heart rate.

1.3.2 Parasympathetic Nervous System

Parasympathetic nerve impulses are relayed to the heart via the right and left vagus (X) nerves (Tortora et al., 2003). The axons of the vagus nerve terminate in the SA node, atrioventricular (AV) node and in the atrial myocardium (Malik & Camm, 1995). The vagus nerve releases Ach from the terminal endings, causing muscarinic Ach receptors to respond with an increase in cell membrane potassium ion conductance during

repolarization, which decreases heart rate by slowing the rate of spontaneous depolarization (Sakmann, 1983).

The response of the SA node to vagal stimulation occurs quickly, with maximum response occurring within 400 msec (Tortora, 2003). This prompt response is a result of the linkage between muscarinic receptor activation and changes in ionic currents being mediated by signaling molecules in the cell membrane rather then via a second messenger signaling pathway (Hille, 1992). Parasympathetic stimulation dominates at rest, but with increasing levels of exercise it declines while sympathetic stimulation is enhanced.

1.3.3 Sympathetic Nervous System

Sympathetic neurons extend from the medulla oblongata to the thoracic region of the spinal cord. From the spinal cord the preganglionic neurons terminate at the sympathetic chain ganglia, where the postganglionic fibers originate (Guyton, 2000). The sympathetic cardiac accelerator nerves extend from the sympathetic chain ganglia to the SA node, AV node, AV conducting pathways as well as the atrial and ventricular myocardium (Malik & Camm, 1995). When the sympathetic system is stimulated, it influences the heart rate via the release of EPI and NE from the adrenal medulla and sympathetic terminal nerve endings (Tortora et al., 2003). EPI and NE bind to β-adrenergic receptors on cardiac muscle fibers to cause an increased rate of spontaneous depolarization and enhanced entry of Ca^{2+} through voltage-gated slow Ca^{2+} channels in contractile fibers (Tortora et al., 2003). This results in an increase in both heart rate and

contractility, respectively, which allows for a greater ejection of blood during systole (Lewis, 2005).

Unlike the rapid response of the heart to vagal stimulation, a latent period of up to 5 seconds can occur following the onset of sympathetic stimulation (Malik & Camm, 1995). This difference in time constants between vagal and sympathetic responses is most likely due to the difference in signaling pathways between the two systems (Hill-Smith & Purves, 1978). While muscarinic stimulation is initiated by signaling molecules within the cell membrane, adrenergic stimulation commences in the membrane and requires second messenger activation of a protein kinase in the cytosol (Hille, 1992). As a result, sympathetic responses are slower with a time delay of a few seconds while there is little delay in vagal responses.

1.4 Heart Rate Variability

1.4.1 Introduction

A normal functioning heart demonstrates considerable variability in the duration of the cardiac cycle. This variability is primarily a result of the influence of the ANS on the rate of depolarization of the SA node (Task Force, 1996). The intervals between sinus rhythms vary due to blood pressure regulation, thermoregulation, respiratory rate, respiratory tidal volume, actions of the RAAS and circadian rhythms (Stein et al., 1994), all of which cause the heart rate to increase or decrease via sympathetic or parasympathetic stimulation.

HRV analysis examines beat-to-beat changes in the R-R interval of heart rate data. The amount that the R-R interval changes in successive cardiac cycles is quantified in HRV analyses, with higher values associated with more functionally efficient cardiac autonomic control mechanisms (Task Force, 1996). HRV analysis is preferred over direct measures of cardiac autonomic nerve activity since the effects of anesthesia and the invasiveness of the procedures limit their applicability to functional contexts (Berntson et al., 1997).

1.4.2 Clinical Applications

In 1965, fetal distress was observed to be preceded by changes in interbeat intervals. Researchers inferred that these variations may be a result of ANS modulation (Hon & Lee, 1965). A large amount of research was completed on HRV from this point on, as it was proven to be associated with many disease states. Wolf and colleagues (1978), provided evidence that associated reduced HRV with a higher risk of post-infarction mortality and Akselrod (1981) was the first to use power spectral analysis (PSA) to evaluate cardiovascular control through HRV. In the late 1980's, Kleiger and associates (1987), conducted a landmark study that identified HRV as a strong predictor of mortality following an acute myocardial infarction. Kleiger and colleagues (1987) observed a large sample of patients after a myocardial infarction and found they had a low standard deviation of the mean R-R interval over a 24 hour period. The relative risk of mortality was 5.3 times higher in this population. It is postulated that these patients are

at risk of ventricular fibrillation due to increased sympathetic and decreased vagal drive to the heart (Kamath & Fallen, 1993).

HRV analysis is currently employed to evaluate ANS modulation of the SA node in patients with a variety of cardiac and non-cardiac diseases (Lombardi, 2002). It is well accepted that decreased HRV is the most powerful ambulatory ECG predictor of cardiac mortality following a myocardial infarction (Kleiger, 2005). HRV is also reduced in patients with coronary artery disease, diabetes, hypertension and as a result of long-term smoking and old age (Kamath & Fallen, 1993).

1.4.3 Frequency Domain Analysis of Heart Rate Variability

Similar to the process of differentiating white light into its individual colours, two heart rate signals can be distinguished from one another by analysis of their relative frequencies (Lewis, 2005). From the surface electrocardiogram (ECG), a tachogram is made by calculating the R-R intervals as a function of the beat number. Subsequently, statistics such as mean, variance and relative frequency distribution are calculated (Pagani et al., 1986). Then PSA is completed, so that the relative frequency or "power" of the constituent frequencies of the heart rate signal to which slower and faster mechanisms contribute can be established (Lewis, 2005). The total variation of the frequency components is expressed in terms of power spectral density (PSD), which depicts spectral power as a function of frequency. Therefore, in each spectrum, individual components are identified by their centre frequency and quantified by their power (Guzetti et al., 1991).

There are a number of technical requirements and recommendations that must be followed when PSA of HRV is carried out in order for the analysis to be reliable and reproducible (Task Force, 1996). The recording environment between and within participants must be the same in order for individual spectral components to be attributed to specific physiological mechanisms (Task Force, 1996). A sampling rate higher than 250 Hz is optimal since a lower sampling rate would produce imprecise estimation of the R wave fiducial point, which would alter the spectrum (Friesen et al., 1990; Pinna et al., 1994). Also, ectopic beats, arrhythmic events, missing data and noise alter PSD of HRV (Task Force, 1996). HRV analysis can not be completed if there are more than 2 or 3 ectopic beats in 5 minutes of data since they cause a short RR interval followed by a long pause, which appears as a sharp spike in the HRV tachogram (Malik & Camm, 1995). Short-term recordings free of noise, ectopic beats and missing data should be utilized for analysis (Task Force, 1996).

Recording lengths must be standardized for both within and among study comparisons. This is because HRV tends to increase with the length of the analyzed record (Saul et al., 1988). Short-term recordings are also preferable in the respect of data stationarity (Malik & Camm, 1995). Acquiring biological signals during a brief amount of time allows greater stability of activity for the participant. Interpretation of frequency analysis over a 24-hour period is less accurate because the LF and HF power components cannot be considered stationary (Furlan et al., 1990).

There are three main spectral components in a short-term recording of 2-5 minutes. These are the very low frequency (VLF), low frequency (LF) and high

frequency (HF) components (Task Force, 1996). The physiological definition of the VLF component is less defined than the other two and it does not have coherent properties (Task Force, 1996). There are some hypotheses that VLF may represent influence of the RAAS as it is reduced 20% through ACE inhibition (Kleiger et al., 2005) and may also reflect thermoregulation and vasomotor activity (Stein et al., 1994). The activity of the parasympathetic system, representing respiratory variation is thought to be primarily responsible for the HF component of HRV (0.15-0.4 Hz) (Pagani et al., 1986). The amplitude of the peak is abolished by atropine and when the frequency of ventilation changes the center of frequency of the HF peak moves according to the ventilatory rate (Kleiger et al., 2005).

The LF component is modulated by both sympathetic and parasympathetic systems and is affected by the oscillatory rhythm of the baroreceptor system (0.04-0.15 Hz) (Stein et al., 1994). The amount of sympathetic activity responsible for the LF component has been examined in studies by using various manipulations. β-adrenergic blockade significantly reduces heart rate and ABP and causes a smaller increase in the LF component caused by standing (Pagani et al., 1986), while atropine practically abolishes the LF peak (Kleiger, 2005). Also, orthostatic challenge such as head-up tilt, which increases sympathetic efferent traffic and decreases vagal outflow (Burke et al., 1977) has provided evidence of increased normalized LF power (Montano et al., 1994). Since LF fluctuations reflect both sympathetic and vagal activity, considering LF power alone is not a true depiction of sympathetic tone. Only when HF is unaffected or affected in the

opposite direction can changes occurring in the LF band be inferred to be of sympathetic origin (Malik & Camm, 1995).

There are two approaches used to quantify cyclic fluctuations of RR intervals. These are the Fast Fourier Transform (FFT) (Akselrod, 1981) and Autoregressive Modeling (AR) (Pagani et al., 1986). AR concentrates on the more significant peaks and attempts to exclude "noise" while FFT includes all data (Berntson et al., 1997). AR is a parametric approach that assumes the time series under analysis is the output of a given mathematical model and does not have any a priori definition of frequency bands. AR analysis produces smoother spectral components with an accurate estimation of PSD and is easy to post process when compared to FFT (Task Force, 1996). A limitation of AR analysis is the model order that describes the signal is not predefined, so the suitability and complexity of the model have to be verified (Kamath & Fallen, 1993).

FFT analysis of HRV is recommended based on easy applicability, computational speed and direct interpretation of the results (Malik & Camm, 1995). However, the HRV signal is a pseudorandom phenomenon and the deterministic natures of the algorithms used for FFT analysis are applicable to periodical phenomena or equally sampled data (Pagani, 1986). Also, they are theoretically based on infinite data sequences, which introduce error in estimates of the true functions (Malik & Camm, 1995). Overall, there are advantages and disadvantages to both AR and FFT analysis of HRV, but comparable results are usually obtained due to their many similarities (Berntson et al., 1997).

1.4.4 Time Domain Analysis of Heart Rate Variability

The standard deviation of mean heart rate, also known as HRV is characterized by descriptive statistics in time domain analysis. This type of analysis is a variable used in prognosis of survivors of an acute myocardial infarction and in congestive heart failure (Kamath & Fallen, 1993). Time domain analysis can be used for short periods of 5 to 30 minutes or long periods up to 24 hours of ECG recordings.

In time domain analysis, each QRS complex is detected from a continuous ECG recording and the normal-to-normal (NN) intervals (all intervals between adjacent QRS complexes resulting from sinus node depolarization) or instantaneous heart rate is determined (Task Force, 1996). There are two classes of statistical time-domain measures that can then be calculated: those derived from direct measures of NN intervals or instantaneous heart rate and those derived from the difference between NN intervals (Task Force, 1996).

Standard deviation of the NN interval (SDNN) and standard deviation of average NN interval (SDANN) are both direct measures of NN intervals (Kleiger et al., 2005). SDNN is the most commonly used statistical time-domain measure because it reflects all the cyclic components responsible for variability in the recording since variance is mathematically equal to total power of spectral analysis. Therefore, it is an estimate of overall HRV (Task Force, 1996). Use of this statistic requires cautious editing to exclude ectopic and missed beats. Also, recordings must be of the same duration since total variance of HRV is augmented as the length of the analyzed recording increases. SDANN is calculated over short periods (5 minutes) over 24 hours; therefore it is an

estimate of long-term components of HRV. SDANN provides a smoother version of SDNN and is less subject to editing error since several hundred NN intervals are averaged (Kleiger et al., 2005).

The square root of the mean squared difference of successive NN intervals (rMSSD) is a statistical time domain measure derived from the difference between NN intervals (Stein et al., 1994). This measure is used as an estimate of short-term components of HRV (Task Force, 1996). The number of interval differences of successive NN intervals greater than 50 ms (NN50) and the proportion derived by dividing NN50 by the total number of NN intervals (pNN50) are additional variables that measure the difference between NN intervals (Stein et al., 1994). These particular time-domain measures allow comparisons to be made between different activities.

Time domain measures are advantageous indices for predicting major cardiac events and for recording circadian variations (Kamath & Fallen, 1993). However, the patients' activities during the recording period cannot be controlled and it is not possible to separate the autonomic signals that influence the SA node as in PSA (Kamath & Fallen, 1993).

1.4.5 Respiratory Sinus Arrhythmia and Heart Rate Variability

Respiratory sinus arrhythmia (RSA) refers to the cyclical fluctuations in heart rate associated with respiration (Malik & Camm, 1995). Katona & Jih (1975) observed that R-R interval fluctuations (RSA) are related to absolute vagal firing rates in anesthetized

dogs with constant breathing rates. Sympathetic and parasympathetic nerve activities fluctuate on a breath-by-breath basis, with RSA mainly mediated through efferent vagal activity (Berntson et al., 1997).

During inspiration, neural activity to the heart increases in the sympathetic fibers, while neural activity in the vagal fibers increases upon expiration (Berne & Levy, 2001). Rhythmic changes in vagal activity are represented in heart rate because Ach released at the vagal endings is removed rapidly, while NE at sympathetic nerve endings is removed slowly. This diminishes the effect of sympathetic activity on the rhythmic variations in heart rate, causing RSA to be a consequence of oscillations in vagal activity (Berne & Levy, 2001).

Evidence from various studies has verified vagal cholinergic influence as the main source of respiratory cardiac dysrhythmia (Askelrod et al., 1981; Pagani et al., 1986; Pomeranz et al., 1985; Saul et al., 1991). Cholinergic blockade or functional vagotomy nearly abolishes RSA but β-adrenergic blockade does not change RSA (Askelrod et al., 1981; Pagani et al,, 1986; Pomeranz et al., 1985). For instance, Pomeranz and colleagues (1985) illustrated that cardiac parasympathetic blockade abolished heart rate fluctuations above 0.15 Hz while sympathetic blockade had little effect on fluctuations above 0.15 Hz. Also, direct vagal stimulation caused nearly identical RSA frequency characteristics as demonstrated in the transfer function (Saul et al., 1991).

The most accepted cause of RSA is through the central nervous system that becomes entrained to the respiratory rate as a result of input from the bronchopulmonary receptors (Malik & Camm, 1995). In heart-lung bypass experiments on animals, the

respiratory center in the medulla has been shown to influence cardiac autonomic centers. When the lungs are collapsed and the venous return is diverted to a pump-oxygenator, rhythmic movements of the rib cage and changes in heart rate at the respiratory frequency are still evident (Berne & Levy, 2001). Various reflexes from receptors in the periphery also contribute to RSA. Intrathoracic pressure decreases during inspiration and causes enhanced venous return to the right side of the heart, which distends arterial receptors in the right atrium to cause an increase in heart rate (Berne & Levy, 2001). An increased pressure in pulmonary veins leads to increased filling of the left atrium (Malik & Camm, 1995). This causes an increase in stroke volume and arterial blood pressure, which reduces heart rate through baroreceptor stimulation (Berne & Levy, 2001).

The influence of breathing on RSA must be controlled and accounted for since the frequency of HF is dependent on the respiratory rate (Kamath & Fallen, 1993). RSA is attenuated with an increase in breathing frequency (Brown, 1993; Kamath & Fallen, 1993). Brown and colleagues (1993) demonstrated that RR interval power at respiratory frequencies significantly decreased as breathing frequency increased and it was also significantly greater at a tidal volume of 1500 ml when compared to 1000 ml. Additionally, breathing at a slow rate caused HF and LF to overlap due to the possibility that sympathetic nerve traffic may contribute to the respiratory frequency R-R interval changes (Brown et al., 1993 & Novak et al., 1993).

There is much debate in the literature as to whether or not breathing rate and depth should be controlled. Hirsch and Bishop (1981), as well as Eckberg (1985), found that both voluntary control of breathing and breathing at a controlled rate produces consistent

R-R interval fluctuations. However, it has been reported that controlled metronomic breathing increases both HRV and R-R intervals (Pagani et al., 1986). It is hypothesized that breathing at a controlled rate may require mental effort and change HRV in the process (Berntson et al., 1997). As a result, it is recommended that respiratory frequency and depth be measured during clinical studies using HRV spectral analysis (Berntson et al., 1997; Brown et al., 1993).

1.4.6 Orthostatic Stress and Heart Rate Variability

HRV is assessed with short-term measurements during maneuvers that challenge the autonomic system such as during standing or passive tilt in controlled laboratory conditions (Kleiger et al., 2005). A change in posture from supine to standing or during passive tilt causes an increase in sympathetic activity to prevent orthostatic hypotension, altering the sympathovagal balance (Malliani et al., 1991). During orthostatic stress there is excessive pooling of blood in peripheral vessels, which reduces cardiac filling pressures (Malik & Camm, 1995). Right and left ventricular stroke volumes decline and heart rate increases secondary to vagal withdrawal and sympathetic stimulation (Cooke et al., 1999).

A number of investigators have examined the effect of passive tilt and standing on PSA of HRV (Bloomfield et al., 1997; Ewing et al., 1980; Fallen et al., 1988; Freitas et al., 1999; Mallani et al., 1991; Montano et al., 1994; Pagani et al., 1984). Pagani and associates (1984), found that LF represents only a small portion of the total variability at rest but becomes predominant with tilting, while HF accounts for a major part of the

variability at rest and is reduced with tilting. Montano and colleagues (1994) looked at PSA of HRV during passive tilt to quantify changes in sympathovagal balance. A 90° tilt incline caused an increase in LF and a decrease in the HF component, with the degree of tilt incline correlated to a significant reduction of R-R interval (Montano et al., 1994). Passive tilt was also found to progressively increase average muscle sympathetic nerve activity (MSNA), SBP and DBP and their spectral powers at HF and LF (Cooke et al., 1999).

Both standing and passive tilt produce a nearly identical decrease in the R-R interval and HF power and an increase in LF/HF ratio consistent with withdrawal of vagal modulation and a shift towards sympathetic predominance (Bloomfield et al., 1997). The difference between the two procedures is there is no rebound bradycardia during tilt (Bloomfield et al., 1997 & Ewing et al., 1980). This lengthening of R-R intervals during standing is mediated by the contraction of abdominal and leg muscles occurring at the beginning of standing (Ewing et al., 1980). Consequently, Pagani and colleagues (1984), selected passive tilt as their physiological maneuver in order to minimize the influence of the muscular effort of active standing on heart rate. Also, passive tilt requires a minimal engagement of central drive, allowing it to fulfill the stationary requirements of PSA (Montano et al., 1994). Therefore, a response to physiological stress, such as passive tilt is a practical method for evaluating the ANS.

1.4.7 Heart Rate Variability in Hypertension

Hypertension is associated with enhanced sympathetic activity and reduced vagal activity (Pagani et al., 1986). In normal controls, LF is a minor portion of variability at rest and it increases during tilting as a result of sympathetic excitation (Pagani et al., 1984). However, in patients with hypertension, LF is already predominant at rest and only increases a small amount with passive tilt (Guzzetti et al., 1988; Pagani et al., 1984).

The 24-hour variations in blood pressure and LF were examined in normotensive and hypertensive individuals (Dassi et al., 1991; Guzzetti et al., 1991). The normotensive individuals had longer R-R intervals and significantly smaller LF values during night than hypertensives (Guzzetti et al., 1991). Also, in hypertensives the reduction in SBP that occurred at night was not accompanied by significant reductions in the LF component, which had similar power values at day and night (Dassi et al., 1991). The difference between day and night LF values was progressively reduced with increasing severity of the hypertensive state (Guzzetti et al., 1991). Therefore, a reduced day-night oscillation in sympathetic activity may be a characteristic of essential hypertension.

Guzzetti and colleagues (1988) observed a significant correlation between the LF component at rest and the severity of hypertension (Guzzetti et al., 1988). These findings, along with the evidence in the studies mentioned earlier in this section, indicate that hypertension is associated with increased sympathetic activity. Hence, PSD of HRV is able to detect alterations in sympathovagal balance of cardiac control in uncomplicated hypertension (Pagani et al., 1984).

1.4.8 Exercise Training and Heart Rate Variability

It has been proposed that the autonomic balance is modified by regular exercise training (Arai et al., 1989). In a cross-sectional study, Dixon and colleagues (1992) illustrated that the resting LF: HF ratio was lower in athletes than controls and the LF: HF ratio recovered to pre-exercise levels faster in athletes (Dixon et al., 1992). In a longitudinal study, HRV was determined by 24-hour Holter recordings in older adults before and after 9 months of 5 hours/week of aerobic exercise at 70% maximal oxygen uptake (Stein et al., 1999). Exercise training increased total HRV in the trained group while there was no change in the control group (Stein et al., 1999).

In a chronic isometric exercise training study, Taylor and colleagues (2003) examined the effect of IHG training 3 times a week at 30% MVC on resting ABP and HRV in hypertensives. After training, SBP, DBP and MABP were significantly reduced and PSA of HRV revealed a decrease in the LF: HF ratio and an increase in HF area (Taylor et al., 2003).

1.5 Hypertension

1.5.1 Classification

A diagnosis of hypertension is made when an individual has a SBP $\geq$ 140 mmHg and/or a DBP $\geq$ 90 mmHg. However, a positive relationship between the risk of cardiovascular disease and blood pressure begins at 115/75 mmHg and doubles with each 20/10 mmHg increase (Pescatello et al., 2004). As a result, a new classification of prehypertension has been defined to identify individuals who have an increased risk for

cardiovascular disease and who could benefit from adopting a healthy lifestyle to reduce their blood pressure. Prehypertension is classified as a SBP of 120-139 mmHg and/or DBP of 80-89 mmHg (Chobanian et al., 2003).

Hypertension is classified as primary or secondary in nature, which refers to the origin of the disease. The majority of cases are primary, which does not have a known cause, whereas there are various causes of secondary hypertension. For example, causes of secondary hypertension include renovascular disease, endocrine disorders such as Cushing's syndrome and primary aldosteronism, as well as coarctation of the aorta (Brooks, 1996).

Moreover, hypertension is further subdivided into three categories, where Stage I is defined as a SBP of 140-159 mmHg and/or a DBP of 90-99 mmHg, Stage II is defined as a SBP of 160-180 mmHg and/or DBP of 100-109 mmHg and Stage III is defined as a SBP $\geq$ 180 mmHg and/or a DBP $\geq$ 110 mmHg (Pescatello et al., 2004).

1.5.2 Pathophysiology

As mentioned previously, the magnitude of ABP at any point in time is determined by CO and TPR. There are a variety of mechanisms in the body that are responsible for determining CO and TPR, which are therefore associated with the development of hypertension. These factors include the SNS, the RAAS, baroreceptor reflexes, vascular responsiveness and arterial compliance (Rao, 2003).

Studies completed with hypertensives provide evidence for the presence of increased sympathetic nerve activity (Grisk et al., 2004). In a study by Goldstein (1983),

an elevated level of plasma EPI levels was evident in hypertensives compared with normotensives, which indicates an elevation in sympathetic function (Goldstein, 1983). Furthermore, numerous studies have also identified increased postganglionic sympathetic nerve activity to the skeletal muscle in primary hypertension (Grassi et al., 1998; Greenwood et al., 1999).

This increased activity of the SNS also influences organ systems responsible for the maintenance of blood pressure (Grisk et al., 2004). Activation of the sympathetic nerves to the kidney was found to cause increases in renin release, renal vascular resistance and tubular sodium reabsorption (DiBona & Kopp, 1997). This is a significant finding since the renal system is not able to increase sodium and water secretion to lower blood pressure when sympathetic renal activity is augmented.

Other possible explanations for augmented sympathetic activity in hypertensives are abnormalities in insulin metabolism and baroreceptor functioning (Brooks, 1996). High blood insulin levels (hyperinsulinemia) increase SNS activity, which elevates ABP by increasing peripheral resistance and CO (Brooks, 1996). Changes in baroreceptor functioning have also been linked to elevated sympathetic activity in hypertensive individuals, as the baroreceptors may reset themselves to a higher level following chronic periods of blood pressure elevation (Ylitalo et al., 1997).

Another aspect of blood pressure regulation that angiotensin II has an impact on is endothelial function. Nitric oxide is released by the endothelium to cause dilation of the arterioles, resulting in a decrease in both peripheral resistance and arterial blood pressure (Higashi & Yoshizumi, 2004). Nitric oxide release is impaired in hypertensive

individuals, resulting in decreased vasodilation in response to stimuli (Raji, 2001). Raji (2001) proposes that one of the mechanisms responsible for the decrease in nitric oxide in hypertensives is due to a nitric oxide-angiotensin II imbalance. An increased level of angiotensin II in the blood is often linked to a decreased bioactivity of nitric oxide (Raji, 2001). Another mediator of vascular responsiveness is endothelin-1, which causes vasoconstriction through endothelin A receptors on vascular smooth muscle cells and is found to be increased in patients with hypertension (Takano & Komuro, 2001).

Hypertension is also associated with decreased arterial compliance as we age (Joyner, 2000). Decreased arterial compliance means that the arteries become stiffer and therefore cannot contract as much during ventricular contraction, which causes primary hypertension and isolated systolic hypertension in the elderly (Joyner, 2000). The mechanisms responsible for decreased arterial compliance may include vascular smooth muscle hypertrophy, replacement of viable cells with connective tissue and increased cross-linking of connective tissue (Joyner, 2000).

1.6 Isometric Exercise

Isometric contractions are different from dynamic exercise due to the fact that there is an application of force but no change in muscle length. Isometric contraction requires a sustained effort that is held at a particular level of intensity for an extended period of time (Shepherd et al., 1981). Whereas dynamic exercise involves the changing of muscle length during the effort and induces SBP and heart rate to increase dramatically, while DBP drops due to the decrease in TPR. Isometric exercise is

accompanied by an increase in heart rate, SBP, DBP and sympathetic nerve activity (Mark et al., 1985). The pressor reflex and central command are two reflexes that are associated with these hemodynamic responses to isometric exercise (Shepherd et al., 1981).

The pressor reflex begins when there is an accumulation of metabolites in the local muscle. These metabolites are not cleared due to the mechanical contraction of the vasculature by the local muscles. Sensory receptors in the area are responsive to these ischemic metabolites and local chemically sensitive muscle afferent nerves signal central command to increase sympathetic drive. This causes systemic vascular constriction, and an increase in inotropy, leading to an increase in heart rate and stroke volume (Shephard et al., 1981). Total systemic vascular resistance is unchanged or increases only slightly, therefore, the increase in ABP is primarily due to the increase in CO (Shepherd et al., 1981). The increase in ABP is dependent on size of the muscle mass involved in the contraction (Seals, 1993).

Another mechanism that has been implicated in affecting hemodynamics during isometric exercise is central command (Mark et al., 1985). There is an immediate increase in heart rate at the onset of isometric exercise. This suggests that there must be a reflex occurring before the accumulation of muscle metabolites, such as a reflex from mechanoreceptors in the active muscles (Shepherd et al., 1981). This would cause activation of the cardiovascular centers by descending central neural pathways that are involved in the initiation of somatomotor activity (Mark et al., 1985).

1.7 Exercise and Hypertension

1.7.1 Effects of Aerobic Training

Engaging in regular physical activity is beneficial as it can increase maximal exercise capacity and favorably modify a number of coronary artery risk factors such as the lipid profile, hypertension, body composition and glucose tolerance (Pederson & Saltin 2005). The ability of exercise to lower resting ABP in hypertensive individuals is well documented. A number of meta-analyses have shown a decrease in SBP and DBP following participation in an aerobic exercise program (Fagard et al., 2001; Whelton et al., 2002). For example, Fagard and colleagues (2001) conducted a meta-analysis of 44 randomized controlled trials assessing the chronic effect of endurance exercise on blood pressure. In all the studies, the median exercise time was 40 minutes (excluding warm up and cool down) and the average training intensity was 65% of maximal exercise performance. Groups were classified as hypertensive if their SBP was $\geq$ 140 mmHg and/or their DBP was $\geq$ 90 mmHg. SBP changed -7.4 mmHg while DBP changed -5.8 mmHg in the hypertensive group (Fagard et al., 2001). This may provide evidence for aerobic exercise being a viable method of treating hypertension. Evidence from randomized, controlled trials involving controlled hypertensives indicate that continuous, moderate-intensity (12-13 on the Borg scale) aerobic activity, 30 minutes or more, on most days of the week is a suitable recommendation for hypertensives (Pescatello et al., 2004).

There are a variety of hypotheses regarding the mechanisms responsible for the decrease in resting ABP after training. Since blood pressure is determined by CO and

TPR, a reduction in one of these factors must be responsible for the change in blood pressure. However, according to Pescatello et al. (2004), resting CO does not change after chronic exercise, so changes in TPR must be the primary mechanism (Pescatello et al., 2004).

According to Poiseuille's law, TPR is proportional to blood viscosity and length of the vessel, but inversely proportional to the fourth power of the radius (Pescatello et al., 2004). Since blood viscosity and the length of blood vessels remain unchanged with aerobic exercise, the vessel diameter is the variable that must be altered with training. Factors that are indicated to be involved in the increase of vessel diameter after aerobic exercise training are a decrease in sympathetic nervous activity, enhanced baroreceptor control, decreased circulating NE, as well as increased vascular responsiveness and arterial compliance (Pescatello et al., 2004).

1.7.2 Effects of Resistance Exercise

The American College of Sports Medicine recommends resistance training as an adjunct to an aerobic-based exercise program for maintaining muscular fitness in healthy adults (ACSM, 1998). Resistance exercise consists of a combination of static and dynamic contractions. The initiation of the movement consists of a static contraction until the muscular force exceeds the weight of the object, then dynamic contractions are used to raise and lower the weight (McCartney, 1999).

Resistance exercise was previously contraindicated for individuals with cardiovascular disease or hypertension due to the large increases in SBP and DBP. The

elevation in ABP results from mechanical compression of the skeletal muscle vasculature, the pressor response as a product of sustained isometric contractions and increased intrathoracic pressure due to the Valsava maneuver (McCartney, 1999). However, recent evidence indicates that resistance exercise training is safe in cardiac rehabilitation programs (Butler et al., 1992; McCartney et al., 1991; Stewart et al., 1998) and may be a possible modality in the treatment of hypertension (Brooks, 1996).

The ability of resistance exercise to decrease resting ABP is uncertain. Several studies have demonstrated that participating in a 3 days/week resistance program will slightly reduce DBP (Harris et al., 1987; Hurley, 1988; Martel, 1999) and SBP (Martel, 1999). However, other resistance training studies of 6 to 16 weeks in duration did not demonstrate any change in resting SBP or DBP (Dunstan et al., 1998; Katz et al., 1992; Van Hoof et al., 1996). A recent meta-analysis completed in an attempt to clarify the effects of resistance training on resting ABP compiled data from 11 randomized controlled studies, whose length ranged from 6 to 30 weeks (Kelley & Kelley, 2000). Training was completed 2 to 5 times per week at 30 to 90 % of 1 repetition maximum. The results indicated a decrease in SBP and DBP of 3 mmHG.

There is limited data proving that resistance training has a significant favorable effect on resting ABP. However, it should be an adjunct to an aerobic training program due to its physiological adaptations, such as improvements in muscular strength, increases in muscle cross-sectional area and the decrease of blood pressure during contractions performed at the same absolute load as prior to training (McCartney et al., 1996). Therefore, although resistance training may not be the preeminent lifestyle intervention

for reducing resting ABP, it is capable of reducing the effort required to complete strength related activities of daily living by increasing dynamic strength and peak exercise capacity.

1.7.3 Effects of Isometric Exercise

Isometric exercise has received much attention recently for its ability to reduce resting ABP. The beneficial effects of isometric exercise on resting ABP was first studied by Kiveloff and Huber (1971) when participants with normal and elevated blood pressure levels performed maximal isometric contractions of the extremities, buttocks and abdomen for 6 seconds, repeated three times, three times a day for five to eight weeks. After training, there was no change in resting ABP evident in the group with normal blood pressure levels. However, there was a decrease in SBP and DBP in individuals with elevated resting ABP levels (Kiveloff and Huber, 1971). These results motivated Buck and Donner (1985) to examine the effect of regular exposure to isometric exercise in occupational settings on the incidence of hypertension. The results indicated that the incidence of hypertension was lower for individuals whose jobs required a moderate or heavy amount of isometric activity. This difference was still evident when age, social class, obesity and the use of alcohol was taken into account by statistical analysis with a multiple logistic regression analysis (Buck and Donner, 1985). The outcome of these early studies indicated that isometric exercise may be a beneficial therapy for hypertensive individuals; however, a randomized, controlled study is necessary to prove the relationship of isometric contractions to the decrease in resting ABP.

Wiley and colleagues (1992) were the first to carry out controlled studies on the effect of isometric contractions on individuals with slightly elevated resting ABP. Participants in the first study had high-normal resting DBP. They trained 3 days per week, completing four 2-minute contractions at 30% maximum voluntary contraction (MVC) using a hand grip dynamometer. In the second study, participants were borderline hypertensive and they performed 4 contractions of 50% MVC held for 45 seconds, completed 5 days per week for 5 weeks. Training resulted in a decrease of SBP by 13 mmHg and DBP by 15 mmHg in the first study and 9.5 mmHg and 8.9 mmHg reductions of resting SBP and DBP respectively was found in the second study. However, when training ended, resting ABP returned to its pre-training value in a similar time period over which the decrease occurred.

A reduction in resting ABP with IHG training has been demonstrated in a number of studies over the past decade and the possible mechanisms responsible for this observation have been examined (McGowan et al., 2006; McGowan et al., 2007; Peters et al., 2006; Ray & Carrasco, 2000; Taylor et al., 2003). One possible mechanism for the hypotensive effect following IHG training is alterations in ANS activity. Both Sinoway et al. (1996) and Somers et al. (1992) examined the effect of forearm endurance training on sympathetic nerve responses. During isometric exercise, the increases in metabolic products stimulate muscle chemosensitive afferents, which cause the activation of the SNS to muscle. Both studies found that endurance forearm training significantly attenuated the increase in the sympathetic nerve response (Sinoway et al., 1996; Somers et al., 1992). These results are most likely due to the decrease in muscle chemosensitive

afferent stimulation, as a result of increased mitochondrial and capillary density and activation of oxidative enzymes (Somers et al., 1992). Sinoway and colleagues (1996) also reported an attenuated increase in MABP, while Somers and colleagues (1992) did not see a change in the blood pressure response during rhythmic forearm training. They attribute this contrasting result to their ability to only collect blood pressure measurements at a rate of once per minute, which is inadequate to detect an attenuation in the blood pressure response (Somers et al., 1992).

The findings of decreased muscle sympathetic nerve activity (MSNA) with endurance forearm training prompted Ray and Carrasco (2000) to examine if IHG training would reduce arterial pressure by attenuating efferent MSNA in a normotensive population. Participants in the training group performed four 3-min contractions at 30% MVC during 4 training sessions for 5 weeks. Resting DBP and MABP significantly decreased in the trained group following IHG training while SBP and MSNA did not change. The lack of change in SBP and the small changes in DBP and MABP (reduction of 5 mmHg and 4 mmHg respectively) were most likely due to the fact that participants were normotensive, unlike previous IHG training studies where the participants had elevated resting ABP. Ray and Carrasco (2000) hypothesized that the decrease in blood pressure at rest was due to peripheral vascular adaptations.

In contrast, Taylor and colleagues (2003) found that changes in ANS activity contributed to the hypotensive effect of IHG training. Hypertensive participants in this study performed four, two-minute isometric contractions at 30% MVC, 3 days a week for 10 weeks. A reduction in SBP, DBP, MABP and resting heart rate was found in the

training group. PSA of HRV and blood pressure variability (BPV) was used to evaluate changes in modulation of the ANS. PSA of HRV showed decreased sympathetic and increased vagal activity, represented by a decrease in low frequency area and an increase in high frequency area, respectively (Taylor et al., 2003). Therefore, these results indicate that a shift in autonomic modulation would explain the reduction in resting ABP after IHG training.

Another mechanism speculated to be responsible for the improvement in resting ABP with IHG training is endothelium-dependent vasodilation. It is well accepted that the production of nitric oxide is important in endothelial-dependent vasodilation. Nitric oxide release is impaired in hypertensive individuals, resulting in reduced vasodilation to stimuli (Raji, 2001). Both Katz and colleagues (1997) and Hornig and associates (1996) investigated the effects of rhythmic handgrip training on endothelial function in individuals with endothelial dysfunction. Both protocols required participants to perform 20 contractions per minute for 30 minutes each day for 8 and 4 weeks respectively. A localized improvement in endothelial-dependent vasodilation but not endothelial-independent vasodilation was found in both studies (Hornig et al., 1996; Katz et al., 1997).

The improvement in endothelial-dependent vasodilation with rhythmic handgrip training led McGowan and colleagues (2006; 2007) to investigate whether this result would also be responsible for the reduction in resting ABP after IHG training (Peters et al., 2006; Ray & Carrasco, 2000; Taylor et al., 2003; Wiley et al., 1992). It was hypothesized that the increase in heart rate and ABP with IHG training would be large

enough to increase systemic pulsatile blood flow and in turn improve systemic vasodilation (Ray & Carrasco, 2000; Taylor et al., 2003). McGowan and associates (2007) examined the effects of bilateral and unilateral IHG training protocols on endothelial-dependent vasodilation and resting ABP. They demonstrated that the bilateral training program improved brachial artery (BA) flow-mediated dilation (FMD) in both arms but the unilateral training program only improved BA FMD in the trained arm (McGowan et al., 2007). This finding implies that IHG training only improves local endothelial-dependent vasodilation. Therefore, a systemic improvement in endothelial dysfunction is not a likely mechanism for the hypotensive effect of IHG training.

The local improvement in endothelial-dependent vasodilation may be a result of an increase in nitric oxide bioavailability due to shear stress, improved antioxidant activity and/or enhanced endothelium-independent vasodilation (McGowan et al., 2006). McGowan and colleagues (2006), investigated whether smooth muscle vasodilation played a role in the improvement of BA FMD following 8 weeks of IHG training. Their results indicate that IHG training improved BA FMD but there was no change in nitroglycerin-mediated maximal vasodilation (an index of endothelium-independent vasodilation) in the trained arm. These results show that the local improvement in BA FMD was not a result of underlying changes in the forearm vasculature (McGowan et al., 2006).

A further potential mechanism that may be responsible for the reductions in resting ABP following IHG training is through improvements in oxidative stress. In an investigation by Peters and associates (2006), blood pressure, blood lipids and markers of

oxidative stress such as whole blood glutathione (GSH), oxidized glutathione (GSSG) and reactive oxygen species (ROS) were measured following endurance exercise. An attenuation of ROS following endurance exercise was evident after six weeks of IHG training and resting GSH: GSSG levels increased 61%, suggesting elevated antioxidant protection (Peters et al., 2006). This decrease in oxidative stress may lead to an increased bioavailability of nitric oxide and a subsequent reduction in resting ABP.

An increase in baroreceptor sensitivity is another mechanism that may be responsible for the decreased resting blood pressure after IHG training. Baroreceptor sensitivity, which is thought to be enhanced by exercise training, has been indicated in the pathogenesis of hypertension (Pescatello et al., 2004). Monahan and colleagues (2000) demonstrated that regular aerobic exercise can attenuate the decline in baroreceptor sensitivity associated with age and can increase sensitivity in men that were previously sedentary. This increased sensitivity in baroreceptor functioning may be a result of changes in arterial compliance (Monahan et al., 2001) or repeated exposure to the pressor response (Raven et al., 2006).

There are numerous potential mechanisms implicated in the reduction of resting ABP following IHG training. These include alterations in modulation of the ANS, as well as changes in endothelium-dependent vasodilation, oxidative stress and/or baroreceptor functioning. Further research is required to conclusively elucidate the exact mechanisms responsible for the improvements in resting blood pressure following handgrip training.

1.8 Summary and Hypothesis

The impact of hypertension on our healthcare system can largely be avoided if our population as a whole made healthier lifestyle choices. The risk factors associated with hypertension such as obesity, physical inactivity, stress, as well as high alcohol and salt intake can all be controlled by lifestyle modifications (WHO, 2003). The ability of IHG training to decrease resting ABP has been verified in several studies (Peters et al., 2005; Ray & Carrasso, 2000; Taylor et al., 2003; Wiley et al., 1992) in both medicated hypertensives and normotensive populations. The ability of IHG training to lower resting ABP in a population of unmedicated, newly diagnosed hypertensives is yet to be determined. Also, there is speculation regarding the exact mechanism associated with the decrease in blood pressure, but no conclusive evidence at this point.

Therefore, the goals of this investigation are two-fold. The first objective is to examine the effectiveness of IHG training in reducing resting ABP in newly diagnosed hypertensive patients, in comparison to matched controls receiving advice from a physician about lifestyle modifications. The hypothesis for this component of the investigation is that 6 weeks of IHG training, in addition to clinically prescribed lifestyle modifications will result in significant reductions in resting ABP in comparison to lifestyle modified controls. The second purpose of this study is to examine markers of autonomic function, specifically, HRV to determine if changes in the ANS exist between the two groups of hypertensive adults. It is hypothesized that the decrease in resting ABP will be associated with a decrease in sympathetic modulation and an increase in parasympathetic modulation of the heart.

2.0 METHODS

2.1 Participants

2.1.1 Recruitment

Hypertensive and prehypertensive participants were recruited from the Hamilton and McMaster community. Patients diagnosed with high blood pressure from McMaster Family Medicine were referred to this study by a physician. They received a letter of information and initially contacted the investigators by phone or email. Also, physicians asked potential participants if they could be contacted by the investigators of this study. If the patient agreed, the physician would forward the name and contact information on to the investigators, who phoned the interested individuals regarding this study. To recruit participants from the McMaster community, an advertisement was placed on the Daily News website and potential participants contacted the investigators by phone or email.

All participants visited the lab on three occasions for blood pressure measurements to determine if they were prehypertensive or hypertensive and therefore eligible for this study. The purpose, study design and testing protocol were explained to each individual upon first visit to the lab. If they still expressed interest and met all the inclusion and exclusion criteria, they were included as a participant in this investigation.

2.1.2 Inclusion and Exclusion Criteria

Participants consisted of both males and females of all ethnicities between the ages of 20 and 70. This age range was chosen to allow for comparison with previous research and also due to the fact that individuals over the age of 70 may have difficulty

completing the IHG training protocol. An individual was eligible for this study if they had an average resting SBP greater or equal to 125 mmHg and/or an average resting DBP greater or equal to 85 mmHg from three readings in our laboratory. Also, participants could not be receiving medication to treat hypertension to be included in this study. Potential participants were asked to fill out a confidential medical questionnaire and were excluded if they were diabetic, on hormone replacement therapy, had heart failure, had arthritis of the hand or were a smoker, since these criteria may distort the measurement of resting ABP.

2.2 Experimental Design

The protocol for this study was completed over a 10-week period for each participant, with the data collected between November 2006 and July 2007. All meetings and testing took place in the Exercise and Metabolism Research Group Lab, McMaster University. The first visit to the lab consisted of an orientation session, where both resting seated and supine blood pressure measures were taken. If the resting ABP values of the participant matched the criteria for this study then they read and signed the consent form (See Appendix A), filled out a medical questionnaire (See Appendix B), leisure time physical activity questionnaire (See Appendix C) and their height and weight were measured. Participants were also given a 3 day diet log to fill out on 1 weekend day and 2 weekdays. The second visit took place during week 2 of the study. During this visit, the first pre- blood pressure measurements were taken in the seated and supine position and familiarization with the testing protocol was completed. Baseline testing was

accomplished during week 3 of the study protocol, after the second pre- blood pressure measurements were obtained.

The third and last pre- blood pressure measurements were attained during the fourth week. At this point, participants were randomized to an intervention group according to their age, baseline blood pressure and gender. Participants returned to the lab for blood pressure measurements each week during the 6-week intervention at approximately the same time to limit changes in resting ABP as a result of daily fluctuations.

The post- measures of resting ABP occurred over 3 sessions spanning a few days apart, following the 6-week intervention. End testing was completed following blood pressure measurements during the first post- visit. A diet log to be filled out on 1 weekend day and 2 weekdays was also given to each participant at this point. During the second post- visit, a leisure time physical activity questionnaire was filled out and height and weight were measured after blood pressure measurements. During the last post- visit, participants whom were not in the handgrip intervention group were offered the opportunity to try isometric handgrip training. Participants were asked to refrain from any vigorous exercise for 24 hours, alcohol or caffeine consumption for 12 hours and from eating any food for the 4 hours prior to each visit to the lab.

2.3 Intervention

2.3.1 Lifestyle Modification Group

Participants randomized to this group were given pamphlets from the Heart and Stroke Foundation regarding lifestyle modifications for reducing blood pressure. The names of the pamphlets they received were: Get Your Blood Pressure Under Control; Take Control: actions to lower your risk; Healthcheck...tells you it's a healthy choice and How fit are you when it comes to managing stress?

Participants were encouraged to read these pamphlets and the information websites listed on them and to follow the guidelines regarding diet, exercise and stress reduction. Each participant had their own log book where they recorded their daily activity during the 10-week protocol.

2.3.2 Handgrip Training and Lifestyle Modification Group

The participants in this group received the same pamphlets as the lifestyle modification group regarding diet, exercise and stress reduction and were encouraged to follow the guidelines in these resources. In addition, this group completed 6-weeks of isometric handgrip training using the Zona Plus Hypertension Relief Device, manufactured by Zona Health, Inc (Boise, ID 83713).

Participants randomized to this group were instructed on the use of the IHG device during their fourth visit to the lab after their third pre- blood pressure measurement. They then completed a handgrip training session in the lab under supervision of an investigator. The next 2 IHG training sessions for week 1 of the

intervention were completed at home and participants were told to contact the investigators by phone or email if they encountered any problems using the device. During their following visit to the lab, participants in this group completed a training session on their own, under observation of an investigator in order to demonstrate their ability to use the handgrip dynamometer. From this point on, the participants completed all of their training at home, 3 times a week for the next 5 weeks.

The training protocol begins with a maximal squeeze with both hands to measure maximum grip strength, with a 10 second rest after each squeeze. The handgrip dynamometer calculates 30% of the MVC, which is the required force of contraction during the training session. Four, two-minute isometric contractions were completed each training session, alternating between hands, with one minute of rest between each contraction. This protocol was based on previous studies (Taylor et al., 2003; Wiley et al., 1992) in which a training response was observed. An LCD screen on the ZonaPlus provided visual and audio feedback, instructing participants to squeeze harder or lighter as needed. Maximum grip strength and an accuracy score was recorded at the end of each training session in a log sheet (See Appendix D). The accuracy score was out of 100, with 100 equal to a perfect score.

2.4 Testing Protocol

2.4.1 Leisure Time Physical Activity Questionnaire

Each participant filled out a leisure time physical activity questionnaire (LTPAQ) before and after the six week intervention. The LTPAQ contained a definition of

moderate and vigorous physical activity and then required each participant to report the days/week and minutes/day they spent engaged in both moderate and vigorous activity over the previous six weeks. The number of minutes spent doing moderate and vigorous activities, both pre- and post- intervention were added up for each participant to verify if there was a change in activity level over the course of the study. The activity level reported in the post- LTPAQ was corroborated by their daily activity logs, which were filled out by each participant during the six week intervention.

2.4.2 Dietary Log and Body Mass Index

Each participant was required to keep a detailed diet record for 2 weekdays and 1 weekend day at the beginning and end of the study. The time of the meal, type of food and portion was recorded for these 3 days. Each food item was input into a diet analysis program (First DataBank Nutritionist Five, San Bruno, CA), which calculated the 3 day average in a diet record nutrient analysis spreadsheet. The protein, carbohydrate and fat intake were recorded both as a percentage of total kilocalories and in grams. Alcohol, fiber and caffeine were recorded in grams while sodium was recorded in milligrams. The 3 day average of kilocalories was also recorded.

Body mass index (BMI) is calculated by dividing weight (kg) by height (m^2). Each participant had their height and weight measured on a floor scale the first and last day of the study. BMI was calculated from these measurements for each participant.

2.4.3 Resting Arterial Blood Pressure Measurement

Participants visited the lab on 12 different days for blood pressure measurements. Pre- intervention measurements took place on 4 of these days, while 5 visits occurred during the intervention phase and post- intervention measurements were taken over the last 3 visits. During each visit to the lab, 4 measures were taken in the seated position and 4 were taken in the supine position. Participants were randomized to either have seated or supine measurements taken first. All measurement of resting ABP took place in a quiet, temperature controlled room after 5 minutes of rest in both the seated and supine position. A blood pressure cuff that was the appropriate size for each individual was positioned on the left arm 2-3 cm proximal to the cubital fossa at the beginning of the rest period. When resting in the seated position participants sat in a chair with back support, with their feet flat on the ground and their arm supported at heart level (Chobanian et al., 2003). The same calibrated Dinamap automatic acquisition system (Pro 100 V2, Critikon Corp., Tampa, FL, USA) was used for all blood pressure measures. Average SBP, DBP, MABP and heart rate were calculated for each visit using the last 3 measurements for both the seated and supine position. For consistency purposes, the same investigator took all pre- and post- resting ABP measurements.

2.4.4 Heart Rate Variability Techniques

2.4.4.1 Protocol

All assessment of HRV took place in a room in the Exercise Metabolism Research Group Lab, McMaster University. The room was quiet and the temperature was kept

constant at 20 to 22°C. The collection of pre- intervention data for HRV analysis was completed during the third visit to the lab for each participant, following a familiarization session which occurred during the second visit. Post- intervention data was collected within a few days of completion of the 6-week intervention. The baseline and end testing data were collected in supine and passive tilt conditions in order to assess autonomic modulation.

Data collection for HRV analysis took place following seated and supine resting ABP measurements. The protocol was explained to each participant before the initiation of data collection. Subjects were then outfitted with 3 ECG electrodes. One electrode was placed below the left clavicle, another below the right clavicle and the last on the left side of the torso below the nipple. A respiratory belt (thoracic belt-UFI, Pneumotrace II) was wrapped around the torso in order to record respiratory rate and depth. The signal from the electrodes and respiratory belt was captured by the Bio Amp CF (Powerlab, AD Instruments) and subsequently sent through an analogue to digital converter (Powerlab 16sp, AD Instruments) at a sampling rate of 1000 Hz per second. The signal was displayed and recorded on Powerlab Chart 5 Software (AD Instruments).

The testing protocol began with data collection during 20 minutes of rest with participants supine on the tilt table (Midland Electric Hi-Lo Tilt Table, model 7208E). In order to minimize artifact in the ECG signal, participants were asked to remain quiet and still without falling asleep. Investigators left the room during collection of resting data, returning periodically to check the quality of the signals. Investigators returned to the testing room following the 20 minutes, at which point participants were tilted to 40° from

horizontal for 10 minutes. Investigators remained in the room during the passive tilt to monitor continuous blood pressure and heart rate measured by photoplethysmography (Finapres blood pressure monitor, Ohmeda 2300). Upon completion of 10 minutes at 40°, participants were further tilted to 60° from horizontal for 10 minutes. Following the 60° passive tilt, participants were lowered to the supine position and disconnected from the ECG, respiration belt and blood pressure monitor.

2.4.4.2 Power Spectral Analysis

Upon completion of HRV data collection, the Powerlab Files were backed up on a zip disk and transferred to a personal computer. The Powerlab files were split up into the resting, 40° tilt and 60° tilt sections and saved as text files so they would be ready for PSA of HRV using MATLAB software. Twenty minutes of resting data and ten minutes of data for both the 40° and 60° tilt were analyzed using PSA for each participant, pre- and post- intervention. However, if the file contained excessive ectopic beats (>5/min), a portion of the file that was ectopic free for at least 3 minutes was analyzed.

The R-R intervals from each steady state recording were divided into 128-second segments. To generate the HRV signal from the ECG recording, the R-wave for each QRS complex was located using a peak-detection algorithm (Pan & Tompkins, 1985) and a continuous R-R interval series was formed; which was re-sampled at a rate of 2 Hz, using linear interpolation, to produce a heart rate signal. Successive 128-second data sets (256 data points) from the heart rate series were analysed using Blackman-Tukey (BT) method (Kay & Marple, 1981) as follows: The mean heart rate was computed for each

128 segment of the data and subtracted. A cosine window was attached to 5% of the signal at each end of the signal to minimize spectral leakage. An autocorrelation function was computed in the time domain. Fourier transform of the tapered autocorrelation function was computed to be the power spectrum of the time domain signal. The LF and HF components of HRV were characterised after identification of the respective peaks in each of the power spectral plots and the associated area under the curve was computed by numerical integration of the curve. From these data, mean HR, mean HF area, mean LF area and mean LF: HF area ratios were computed for each 128 second segment. The total area under the power spectral curve was used as the reference and percentage area generated by the LF and HF components were determined from the total power. Absolute power spectral values for area were expressed as $(bts/min)^2/Hz$. Thereafter, successive data from the power spectra data were averaged and mean LF area, HF area, LF:HF ratio, % LF area, % HF area were obtained for the supine rest, as well as the 40° and 60° tilt conditions. This software was written in MATLAB language. Abnormal beats were interpolated with an interpolation algorithm (Malik & Camm, 1995). The software for the present study has been used in previous investigations (Bajwa et al., 1997 & Ditor et al., 2005).

The HRV indices reported in this investigation include LF area, HF area, LF: HF ratio, % LF area and % HF area. These indices were compared pre- and post-intervention to examine if there would be a change in the HRV response since the LF component is often elevated and the HF component is decreased in individuals with hypertension when compared to healthy normotensive individuals.

2.5 Statistical Analysis

Differences of resting ABP levels between the IHG training group and the lifestyle modification only group were determined by a two-factor (Group x Time) analysis of variance (ANOVA) with repeated measures over time. SBP, DBP, MABP and HR were all compared pre- to post- intervention.

A two-way ANOVA with repeated measures was also used to evaluate heart rate variability data. Group was the first independent variable and time was the second condition (baseline and end testing).

All significant differences between the groups were examined using Tukey's Honestly Significant Difference (HSD) post hoc analysis. An alpha level of <0.05 was regarded as statistically significant.

3.0 RESULTS

3.1 Participant Characteristics

A total of 15 participants enrolled in the study, with 14 completing the protocol to the end. There were 8 participants who participated in the isometric handgrip training group and 6 individuals in the control group. Participant demographics regarding age, gender and resting baseline blood pressure are displayed in Appendix E.

3.2 Effects of Training on Cardiovascular Measures

3.2.1 Systolic Blood Pressure

Absolute Change

Statistical analysis of SBP for the IHG trained group and control group was performed at two testing points (pre and post) and did not reveal any significant GROUP x TIME interaction effects or main effects for TIME or GROUP. Resting SBP values for the IHG group before training and after training were 140.4 ± 4.3 mmHg and 140.7 ± 3.7 mmHg respectively. The control group resting SBP values were 138.0 ± 3.8 mmHg at the pre- and 135.2 ± 5.1 mmHg at post-. SBP for baseline, week 1 through 6 and post-intervention are presented in Figure 1.

3.2.2 Diastolic Blood Pressure

Absolute Change

As seen in Figure 2, statistical analysis of resting DBP for the IHG trained group and control group did not reveal any significant GROUP x TIME interaction effect or

main effects for TIME or GROUP. Therefore, DBP was unaltered in both the trained and control groups. Resting DBP values for the IHG trained group were 82.4 ± 2.8 mmHg and 84.5 ± 2.9 mmHg at the pre- and post- measurements respectively. The corresponding values for the control group were 82.3 ± 3.6 mmHg and 81.0 ± 4.4 mmHg.

3.2.3 Mean Arterial Blood Pressure

Absolute Change

A two-way ANOVA with repeated measures was performed at two time points (pre and post). No significant GROUP x TIME interaction effect or main effects for TIME or GROUP were identified. As seen in Figure 3, MABP values for the IHG trained group were 103.4 ± 2.6 mmHg at the pre- and 104.6 ± 2.7 mmHg at the post-measurements. MABP values for the control group were 102.6 ± 3.0 mmHg and 100.3 ± 4.1 mmHg at the pre- and post- measurements respectively.

3.2.4 Heart Rate

Statistical analysis of resting heart rate revealed a main effect for TIME ($F(1,12)=8.34$; $p<0.02$). As illustrated in Figure 4, the heart rate of the training group demonstrated a decrease that was not significant from 66 ± 4 beats/min before training to 64 ± 3 beats/min after training. The control group also showed a reduction in heart rate that was not significant following the intervention period (71 ± 3 beats/min to 68 ± 3 beats/min). Analysis did not reveal any significant GROUP x TIME interaction effect or main effect for GROUP.

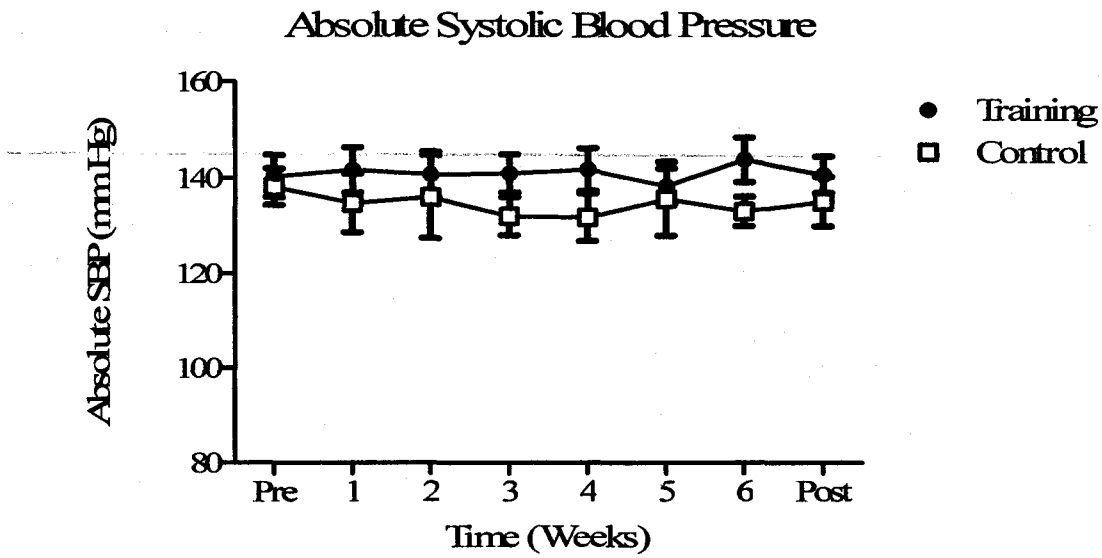

Figure 1. Absolute systolic blood pressure in the handgrip trained group (n=8) and control group (n=6). Values are shown as means ± (SE) from baseline measurements through the six week intervention period to post- measurements. All values are an average of both supine and seated values, with the baseline and post- values an average of three visits.

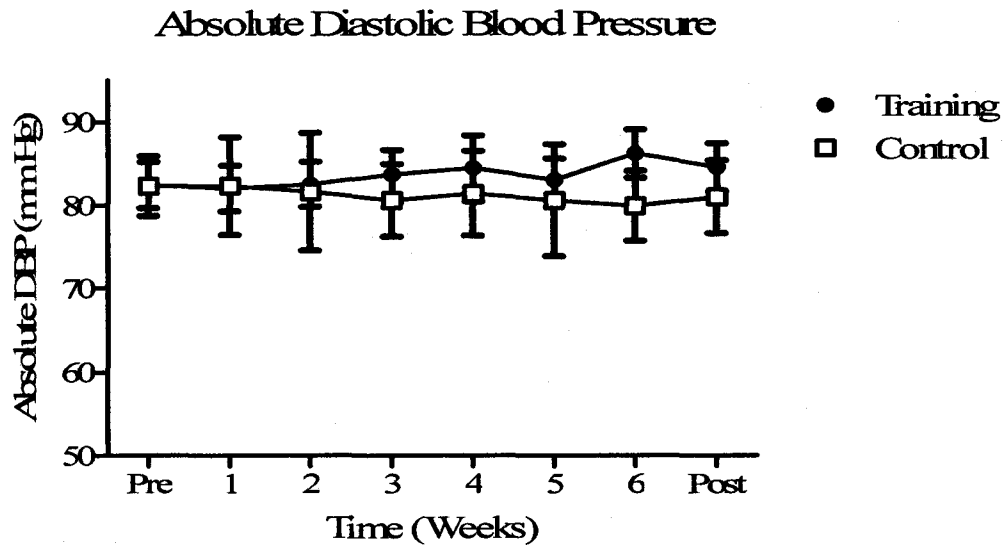

Figure 2. Absolute diastolic blood pressure in the isometric handgrip trained group (n=8) and the control group (n=6). Values are depicted as means ± (SE) from baseline through to post- intervention measurements. All values are an average of both supine and seated values, with the baseline and post- values an average of three visits.

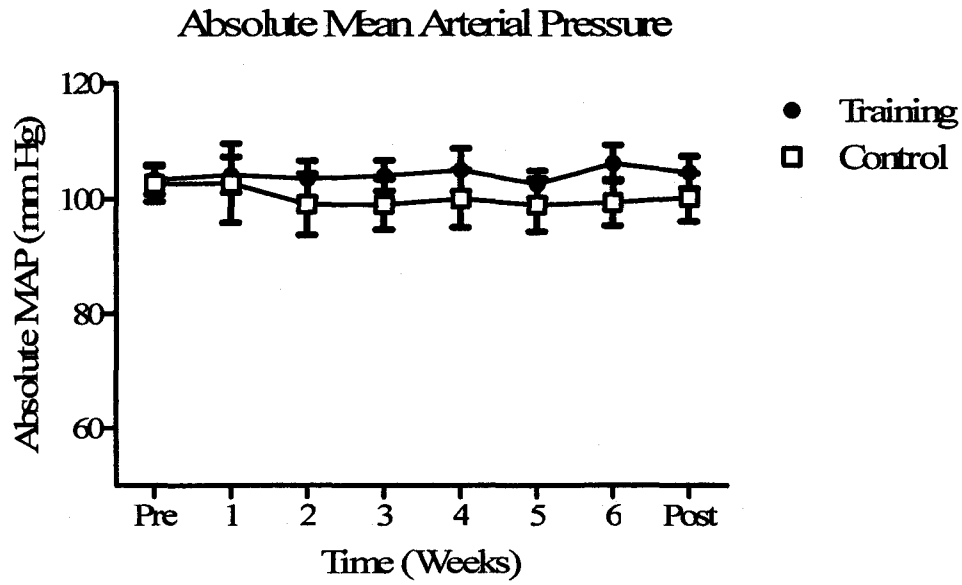

Figure 3. Absolute mean arterial blood pressure in the isometric handgrip trained group (n=8) and the control group (n=6). Values are depicted as means ± (SE) from baseline through to post- intervention measurements. All values are an average of both supine and seated values, with the baseline and post- values an average of three visits.

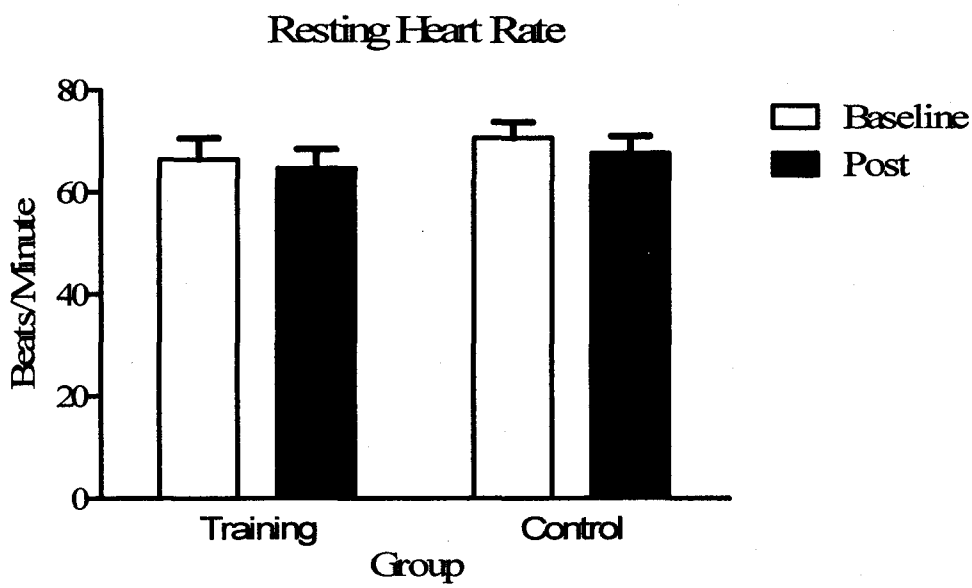

Figure 4. Resting heart rate responses for the IHG trained group (n=8) and the control group (n=6). Values for heart rate are shown as means ± (SE) before and after the 6 week intervention.

3.3 Effect of Training on Heart Rate Variability at Rest

3.3.1 % LF area and HF area

Analysis of % LF area at rest did not reveal a significant change in the training group (62.3 ± 5.3% to 62.8 ± 6.3%), while there was a trend toward reduction in the control group (59.9 ± 9.5% to 54.9 ± 11.8%) (See Figure 5). Similarly, as illustrated in Figure 6, analysis of % HF area at rest was not altered by training (37.7 ± 5.3% to 37.2 ± 6.3%), while the control group demonstrated an increase that was not significant (40.1 ± 9.5% to 45.1 ± 11.8%).

3.3.2 LF area, HF area and LF:HF area ratio

LF area analysis with a two-way ANOVA did not reveal a change for the trained group (157.3 ± 13.6 $(beats/min)^2/Hz$ to 158.8 ± 16.2 $(beats/min)^2/Hz$), whereas, a trend toward reduction was evident in the control group (150.3 ± 24.0 $(beats/min)^2/Hz$) to 138.1 ± 30.0 $(beats/min)^2/Hz$). Analysis of HF area showed no alteration for the trained group (94.7 ± 13.1 $(beats/min)^2/Hz$ to 93.9 ± 15.8 $(beats/min)^2/Hz$) and a slight increase that was not significant in the control group (100.3 ± 23.8 $(beats/min)^2/Hz$ to 112.6 ± 29.1 $(beats/min)^2/Hz$). Additionally, analysis of the LF:HF area ratio for the training group and control group did not reveal a change of statistical significance (2.3 ± 0.8 to 2.5 ± 0.8 and 2.0 ± 0.6 to 2.5 ± 1.4, respectively) (see Figure 7).

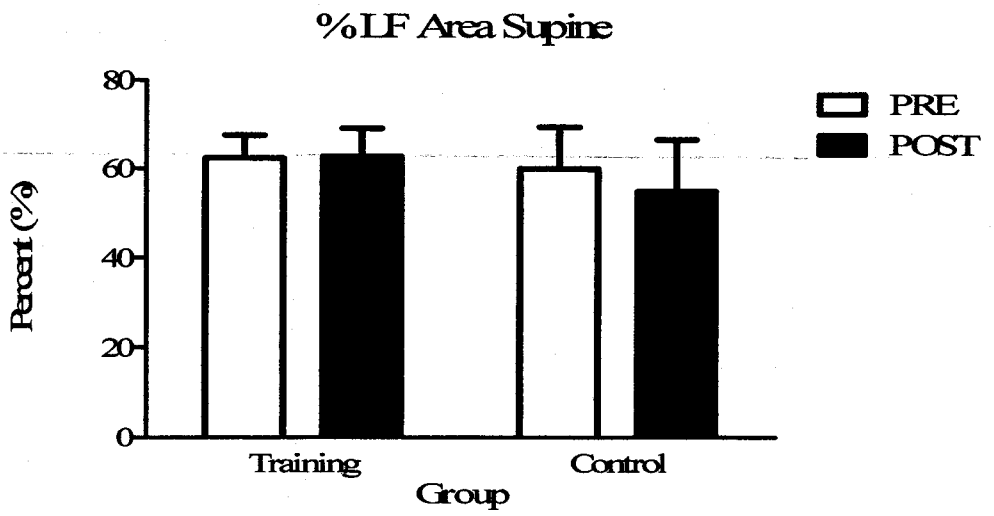

Figure 5. Percent low frequency area of heart rate variability while at rest for the IHG trained group (n=8) and control group (n=5). Values are expressed as means ± (SE) before and after the intervention.

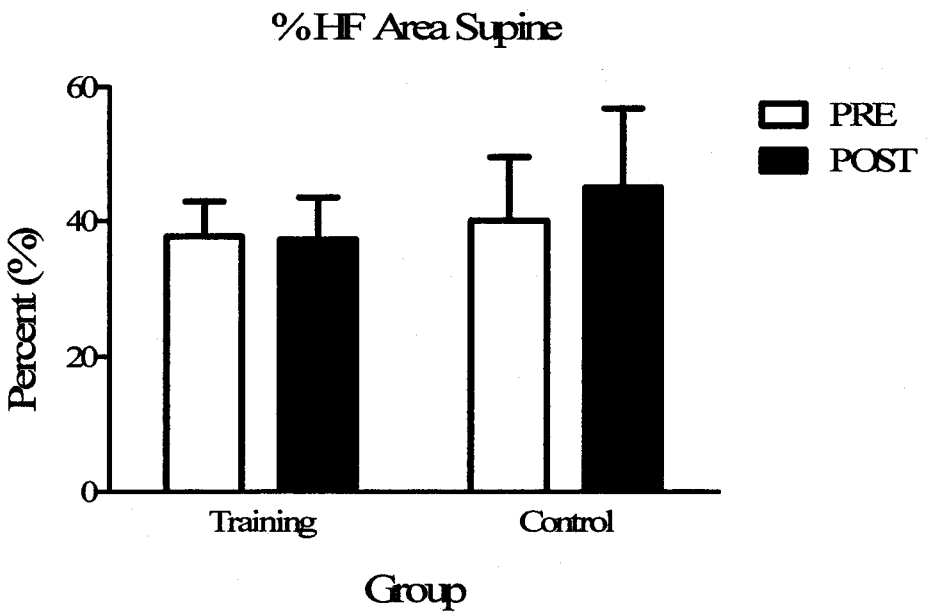

Figure 6. Percent high frequency area of heart rate variability while at rest for the IHG trained group (n=8) and control group (n=5). Values are expressed as means ± (SE) before and after the intervention.

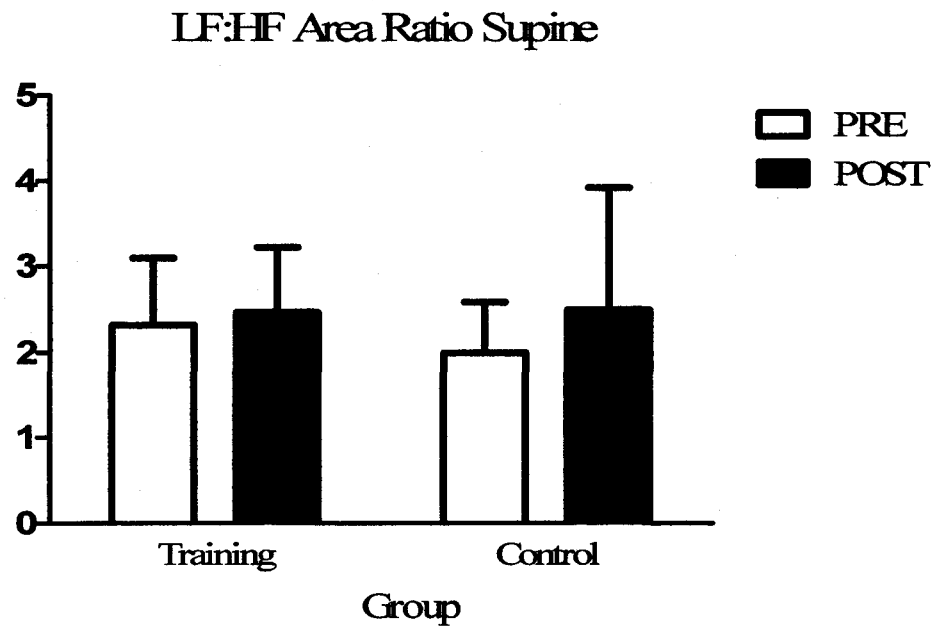

Figure 7. Low frequency to high frequency area ratio of heart rate variability for the IHG trained group (n=8) and control group (n=5). Values are expressed as means ± (SE) before and after the intervention.

3.4 Effect of Training on Heart Rate Variability during Head-Up Tilt

3.4.1 % LF area and HF area

As illustrated in Figure 8, analysis of % LF area during tilt did not reveal a significant change in either the trained or control group after the intervention. The % LF area went from 75.9 ± 6.7% to 77.0 ± 6.6% and 70.9 ± 12.6% to 76.5 ± 8.6% in the trained and control group respectively. Analysis of % HF area demonstrated no change in the trained group (24.1 ± 6.7% to 22.9 ± 6.6%) and a slight decrease that did not reach statistical significance in the control group (29.1 ± 7.9% to 23.5 ± 8.6%) (See Figure 9).

3.4.2 LF area, HF area and LF:HF area ratio

Statistical analysis of LF area revealed a slight increase in both the trained and control group that was not significant. LF area changed from 192.7 ± 17.3 $(beats/min)^2/Hz$ to 195.8 ± 17.1 $(beats/min)^2/Hz$ in the trained group and 185.7 ± 34.1 $(beats/min)^2/Hz$ to 192.8 ± 22.7 $(beats/min)^2/Hz$ in the control group. There is no change in HF area in the trained group after the intervention (60.9 ± 16.9 $(beats/min)^2/Hz$ to 58.0 ± 16.5 $(beats/min)^2/Hz$) and a slight decrease that is not significant in the control group (72.2 ± 30.4 $(beats/min)^2/Hz$ to 58.1 ± 20.4 $(beats/min)^2/Hz$). After the intervention period, the head-up tilt produced a slight increase in LF:HF area ratio that was not significant in the trained group (5.5 ± 1.4 to 5.9 ± 1.4). Conversely, analysis revealed a decrease in the LF:HF area ratio in the control group that did not reach statistical significance (7.0 ± 2.4 to 4.7 ± 1.0) (see Figure 10).

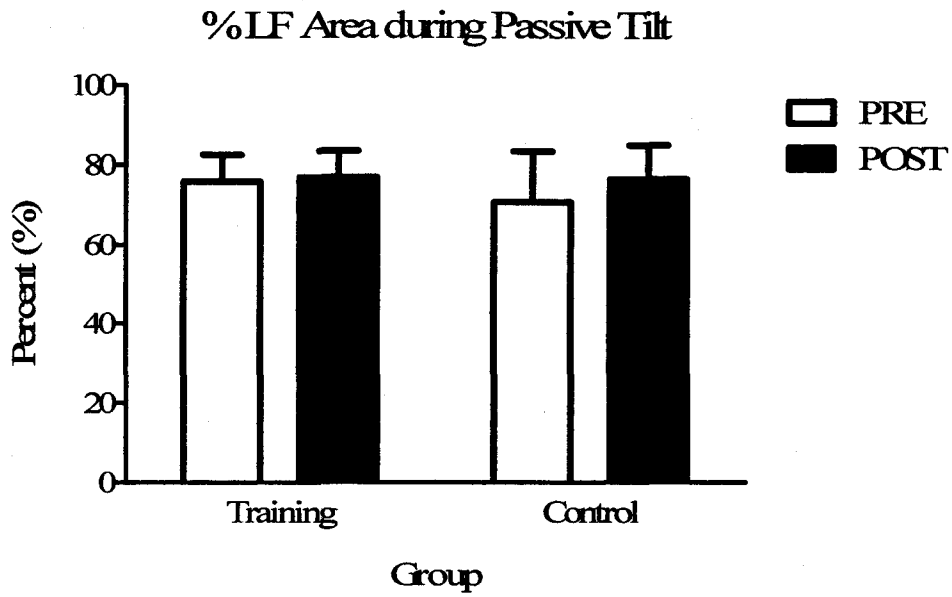

Figure 8. Percent low frequency area of heart rate variability during passive tilt for the IHG trained group (n=8) and control group (n=5). Values are expressed as means ± (SE) before and after the intervention.

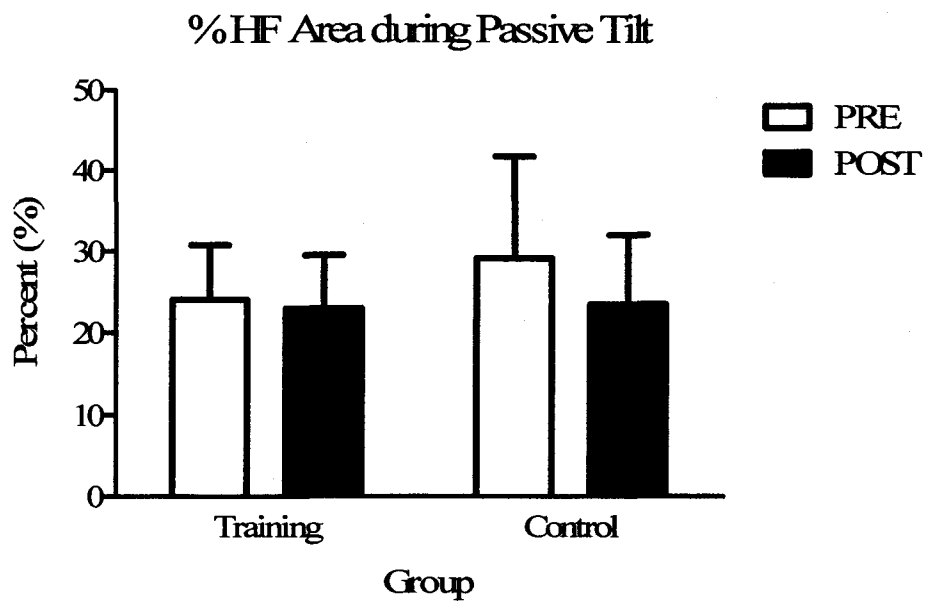

Figure 9. Percent high frequency area of heart rate variability during passive tilt for the IHG trained group (n=8) and control group (n=5). Values are expressed as means ± (SE) before and after the intervention.

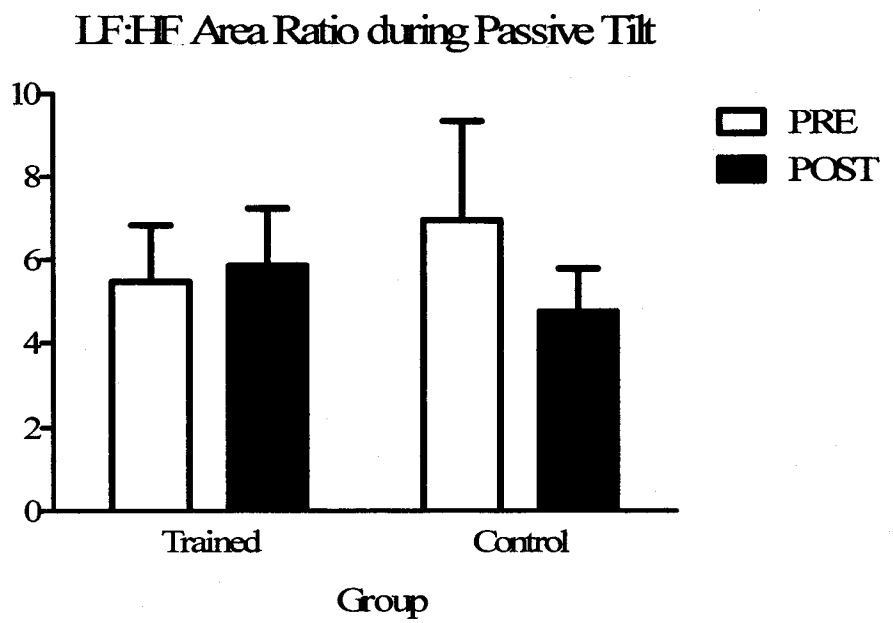

Figure 10. Low frequency to high frequency area ratio of heart rate variability for the IHG trained group (n=8) and control group (n=5) during passive tilt. Values are expressed as means ± (SE) before and after the intervention.

3.5 Nutrient Analysis

Statistical analysis was performed on three-day diet records completed before and after the six week intervention. The analyses revealed a trend for reduction of average calorie (1674.3 ± 151.8 kcal to 1477.5 ± 125.2 kcal) and sodium intake (2337.6 ± 349.1 mg to 2114.50 ± 267.6 mg) in the control group that was not significant. A slight decrease that did not reach statistical significance was also demonstrated for weight (85.5 ± 11.1 kg to 83.9 ± 10.8 kg) in the control group.

On the other hand, analyses revealed slight increases that were not of significance for average calories (1602.8 ± 92.2 kcal to 1712.1 ± 147.8 kcal), sodium intake (2028.0 ± 326.8 mg to 2108.3 ± 340.8 mg) and weight (73.5 ± 4.7 kg to 73.8 ± 4.7 kg) in the trained group.

3.6 Participation in Leisure Time Physical Activity

It was revealed through analysis that the total time spent participating in moderate and strenuous physical activity increased in both the trained and control group, but did not reach statistical significance. The trained group increased their activity time from 189 ± 21 min to 233 ± 35 min, while the control group increased their time engaged in physical activity from 120 ± 44 min to 176 ± 49 min.

4.0 DISCUSSION

The main purpose of the present study was to examine the ability of IHG training to lower resting ABP in newly diagnosed hypertensive individuals, versus the usual advice from physicians about lifestyle modifications. The secondary purpose was to determine if the reduction in resting ABP was related to changes in the ANS, specifically, a decrease in sympathetic modulation and an increase in parasympathetic modulation of the heart. Contrary to our hypothesis, IHG training did not significantly reduce resting ABP and modulation of the autonomic nervous system was not improved by IHG training.

4.1 Effects of Training on Resting Arterial Blood Pressure and Heart Rate

This is one of only a few studies that did not observe a significant reduction in SBP and/or DBP following IHG training. The majority of studies examining the ability of IHG training to decrease resting ABP have demonstrated a decrease in SBP and/or DBP (Peters et al., 2005; Ray & Carrasso, 2000; Taylor et al., 2003; Wiley et al., 1992). The investigation by Wiley and colleagues (1992) employed a treatment regimen similar to the training protocol used in this study. Participants were borderline hypertensive and trained 3 days per week, completing four 2-minute contractions at 30% MVC using a hand grip dynamometer. Training resulted in a decrease of SBP by 13 mmHg and DBP by 15 mmHg (Wiley et al., 1992).

However, there are a few alterations in the protocol of the present investigation that may explain why there is a variation in the results compared to other IHG training

studies (Peters et al., 2005; Ray & Carrasso, 2000; Taylor et al., 2003; Wiley et al., 1992). The purpose of this study was to investigate whether IHG training, along with lifestyle modifications, is a suitable therapy for physicians to recommend to non-medicated hypertensives. In order for the results to be applicable to a clinical setting, participants completed only 2 IHG training sessions under the supervision of an investigator. The remaining 16 training sessions were home-based, with participants recording their IHG training scores in a log book. This is the first home-based IHG training study. In previous investigations, IHG training took place in a laboratory setting, supervised by a trained investigator. The number of supervised exercise sessions in prior studies varied from 18 to 30, depending on the protocol of the investigation (Peters et al., 2005; Ray & Carrasso, 2000; Taylor et al., 2003; Wiley et al., 1992).

Various studies have examined exercise capacity and an assortment of physiological factors in supervised versus home-based exercise programs (Karapolat et al., 2007, Patterson et al., 1997 & Regensteiner et al., 1997). Karapolat and colleagues (2007) recruited heart transplant patients and randomly assigned them to a hospital-based or home-based exercise program (Karapolat et al., 2007). The program was 8 weeks long, with exercise sessions 3 times per week that consisted of flexibility, aerobic and strength exercises. The home-based group was taught the exercises by a physiotherapist at the beginning of the study. The investigators found that the hospital-based group increased their Peak VO_2 from 16.73 ± 3.91 mL/kg/min to 19.53 ± 3.89 mL/kg/min, while there was no change in VO_2 in the home-based exercise group (20.12 ± 4.40 mL/kg/min to 19.48 ± 4.53 mL/kg/min) (Karapolat et al., 2007).

Similarly, Regensteiner and colleagues (1997) examined whether hospital-based and/or home-based exercise rehabilitation programs resulted in improvement of functional status for patients with claudication due to peripheral arterial disease (Regensteiner et al., 1997). The hospital-based patients attended 3 exercise sessions lasting a total of 1 hour, while the home-based patients were instructed to walk 3 times per week and were contacted weekly by an investigator who provided encouragement. The results indicated that the supervised exercise program was superior to the home-based program, as participants in the supervised program were able to increase their peak walking time by 137%, while there was no change in the home-based group (Regensteiner et al., 1997). These results indicate that a home-based, unsupervised exercise program may not be as successful as a supervised exercise program, potentially explaining the differing results of the present IHG training study to those carried out previously (Peters et al., 2005; Ray & Carrasso, 2000; Taylor et al., 2003; Wiley et al., 1992).

Another factor that may have contributed to the non-significant findings for resting ABP in the IHG trained group was the power of the investigation (n=14). Only 8 participants were recruited for the training group and 6 for the control group. In addition, 2 participants in the training group experienced an increase in SBP by ~9 mmHg over the course of the study, perhaps due to new musculoskeletal pain and the increase of anti-inflammatory drugs. One individual was experiencing pain from osteoarthritis in the hip and the other from sciatica towards the end of the investigation. Jin and colleagues (2007) measured MABP in mice with a chronic constriction injury of the sciatic nerve

and found that MABP was elevated by ~13 mmHg for a period of two weeks after the onset of pain. This finding demonstrates that sciatica pain may be responsible for the increase in resting ABP in this particular participant (Jin et al., 2007).

Similarly, an increase in the use of nonsteroidal anti-inflammatory drugs (NSAIDs) has been demonstrated to increase resting ABP (Hochman, 2007 & Pope et al., 1993). Meta-analyses of the effect of NSAIDs on cardiovascular parameters revealed that many drugs within the NSAID class are capable of increasing MABP by as much as 5 mmHg (Johnson, 1997 & Pope, 1993). Also, individuals taking a NSAID agent had an increased risk of 40% for receiving a diagnosis of hypertension when compared to non-NSAID users. NSAIDs are responsible for an increase in resting ABP due to their inhibitory effect on the vasodilatory benefits of prostacycylin, which causes an increase in vascular resistance and subsequently, MABP (White, 2003).

In the present study, a trend for reduction in resting SBP was evident in the control group (138.2 ± 3.8 mmHg to 135.2 ± 5.1 mmHg). Although this group was not completing IHG training, they were attempting to lower their resting ABP by various lifestyle modifications. The control group succeeded in reducing total calorie intake, which resulted in a small decrease in weight (85.5 ± 11.0 kg to 83.9 ± 10.8 kg). Resting SBP has been shown to be correlated with weight and weight loss in epidemiological studies (Paffenbargar et al., 1983). For instance, in a study by Reisen and colleagues (1987), overweight men and women were placed on a weight-reduction program without salt restriction for 6 months. By the end of the study, each participant had lost at least 3 kg, and all but 2 had reduced their resting ABP (Reisen et al., 1987). In a similar study

with unmedicated hypertensives, a weight loss of 1.8 kg was associated with a 4.4 mmHg and 4.3 mmHg decrease in SBP and DBP, respectively (Blumenthal et al., 2000).

An additional explanation for the reduction in resting SBP in the control group is the trend for a decrease in salt intake (2337.6 ± 349.1 mg to 2114.5 ± 267.6 mg). In a meta-analysis of 23 trials completed by Cutler and colleagues (1991), blood pressure declines in hypertensives were 4.9 ± 1.3 mmHg and 2.6 ± 0.8 mmHg for SBP and DBP respectively, for reductions in urinary sodium excretion ranging from 16 to 171 mmol/24 hour period in individual trials (Cutler et al., 1991). Therefore, the decrease in sodium intake, in combination with weight loss in the present study is one likely explanation for the ~3 mmHg reduction in SBP in the control group.

Resting heart rate decreased 2 beats/minute (66 ± 4 beats/min to 64 ± 4 beats /min) and 3 beats/minute (71 ± 3 beats/min to 68 ± 3 beats/min) in the trained and control group respectively. This finding is similar to previous IHG training studies, where heart rate demonstrated a 2 beat/minute decrease in the trained group (Taylor et al., 2003 & Wiley et al., 1992). The heart rate reduction is most likely a result of increased endurance exercise and the associated enhanced vagal tone (Shi et al., 1995). The trained group increased their activity time from 189 ± 21 min to 232 ± 35 min, while the control group increased their time engaged in physical activity from 120 ± 44 min to 176 ± 49 min.

4.2 Effects of Training on Heart Rate Variability

PSA of HRV was used to assess autonomic function before and after the 6-week intervention in the present study. Decreased HRV occurs in patients with coronary artery

disease, diabetes, hypertension and is a predictor of cardiac mortality following a myocardial infarction (Kamath et al., 1993 & Kleiger, 2005). PSA of HRV yields the relative frequency or "power" of the constituent frequencies of the heart rate signals (Lewis, 2005). The activity of the parasympathetic system is thought to be primarily responsible for the HF component of HRV, while the LF component is reflective of sympathetic activity for the most part and is affected by the oscillatory rhythm of the baroreceptor system (Stein et al., 1994).

In individuals with normal resting ABP, HF is predominant and LF represents only 30% of total variability at rest (Pagani et al., 1984). During sympathetic stimulation, such as during passive tilt, LF becomes larger, while HF decreases (Guzetti et al., 1988). However, this pattern is different in individuals with elevated blood pressure. Various investigations have identified an elevated LF and reduced HF in hypertensives when compared to normotensives, indicating sympathetic predominance while at rest in hypertensive individuals (Guzzetti et al., 1991, Langewitz et al., 1994 & Pagani et al., 1984). Also, since LF is already elevated in hypertensives at rest, sympathetic stimulation produces smaller changes in LF and HF (Guzzetti et al., 1991). Guzzetti and colleagues (1991) found the resting LF values and the effects of tilt on LF and HF to be significantly correlated with the severity of the hypertensive state (Guzzetti et al., 1991). PSA revealed similar characteristics of HRV for participants in the present study as those found by Guzetti and colleagues (1991), as the LF power was greater than HF power at rest for the majority of participants in this study.

Endurance exercise training has demonstrated the ability to alter resting measures of HRV (Stein et al., 1999 & Tulppo et al., 2003). Training 6 times per week for 8 weeks at an intensity of 70-80% of maximum heart rate significantly increased the HF component and decreased the LF component, resulting in a reduced LF: HF ratio (Tulppo et al., 2003). In an IHG training study, performing isometric contractions for 2 minutes, twice in each arm, 3 times per week at 30% MVC significantly increased the HF area and there was a trend for reduction of the LF area and LF:HF area ratio (Taylor et al., 2003). However, in the present study, there was no change in autonomic modulation following IHG training. During rest, there was no change in the HF or LF area between the pre- and post- intervention visits. During passive tilt, the LF area increased and HF area was reduced both before and after the intervention. However, there was no difference in the responses between the two visits. One potential explanation for the lack of alteration in HRV may be due to the fact that unlike the IHG program of Taylor and colleagues (2003), this training program was home-based and not supervised. As mentioned previously, home-based exercise programs may not be as successful as those under supervision of an investigator (Karapolat et al., 2007, Patterson et al., 1997, Regensteiner et al., 1997). Another possible reason for the differing results may be the length of the study. The present study was 6 weeks in length, while the previous trial which found alterations in autonomic modulation following IHG training was 10 weeks (Taylor et al., 2003).

Conversely, there were trends for alteration in HRV for participants in the control group, who were following lifestyle modification recommendations given to them by

their physician. The % HF area increased from 40.1 ± 9.5% to 45.1 ± 11.8%, while there was a trend for reduction in % LF area, which went from 59.9 ± 9.5% to 54.9 ± 11.8%. The favorable changes in autonomic modulation evident in the control group are most likely due to the decrease in weight (Facchini et al., 2003 & Poirier et al., 2003) and increase in physical activity in this group (Stein et al., 1999 & Tulppo et al., 2003).

Due to time constraints of participants in this study, a second recording of hemodynamic variables before the intervention phase was not feasible. As a result, the reproducibility for PSA of HRV data during repeated trials could not be assessed. However, the program used for PSA has been used in previous investigations (Bajma et al., 1997 & Ditor et al., 2005) and all technical requirements for the use of HRV analysis in a clinical setting (Task Force, 1996) were adhered to in this study. Specifically, the recording environment was unchanged between visits, sampling of data was done at 1000 Hz, when 2 or more ectopic beats were found in 5 minutes of data they were edited out and recording was short-term, which is preferable for data stationarity (Malik & Camm, 1995). Subsequently, the HRV data meets the following criteria identified by Kamath and colleagues (1988): the response to physiological stress, such as passive tilt, should alter sympathovagal balance in a predictable manner and the results for PSA of HRV should correspond with sympathetic and parasympathetic branches of the ANS. The data in the present study meet both of these criteria, as LF area increased upon passive tilt, which was predictable according to similar investigations (Guzzetti et al., 1991; Langewitz et al., 1994 & Pagani et al., 1984) and the centre frequency for the power spectrum corresponded to the sympathetic and parasympathetic branches of the ANS for

each individual. As a result of meeting the criteria outlined above, the applicability of the HRV spectral indices in the present study to clinical situations is sufficient.

4.3 Potential Mechanisms for the Reduction in Resting Arterial Pressure

The present clinical investigation aimed to determine possible mechanisms by which IHG training could decrease resting ABP. Although we did not find reductions in ABP in the present study, possible mechanisms for the reductions reported in previous studies include: alterations in the ANS (Taylor et al., 2003); increase in baroreceptor sensitivity (Wiley et al., 1993); and a decrease in oxidative stress (Peters et al., 2006). A change in autonomic modulation was examined in the present study, while baroreceptor sensitivity was looked at in collaboration with another investigator (Stuckey et al., 2007).

Modulation of the ANS was examined in the present investigation as sympathetic activity is a large contributor to the control of blood pressure through changes in peripheral resistance. In previous investigations, an increase in sympathetic activity has been identified in hypertensive individuals (Grassi et al., 1998; Greenwood et al., 1999). If sympathetic activity is attenuated, then less NE is released and arteriolar smooth muscle is able to dilate (Brooks et al., 1996). This would lead to a decrease in peripheral resistance and an overall reduction in blood pressure.

A reduction in baroreceptor sensitivity has been indicated as a mechanism responsible for the pathogenesis of hypertension (Pescatello et al., 2004). Both arterial compliance and baroreceptor sensitivity were identified to be lower in hypertensive patients when compared to normotensive individuals (Lage et al., 1993 & Potts et al.,

1998). However, Monahan and colleagues (2000) demonstrated that regular aerobic exercise can attenuate the decline in baroreceptor sensitivity associated with age and increase sensitivity in men that were previously sedentary (Monahan et al., 2000). An explanation that has been proposed for the increase in baroreceptor functioning following IHG training involves the cyclic increase in SBP and DBP during training. Repeated exposure to the pressor response may stimulate baroreceptor resetting (Wiley et al., 1993) and increase baroreceptor sensitivity (Raven et al., 2006).

Therefore, there is evidence in the literature that a change in autonomic modulation of the ANS and an increase in baroreceptor sensitivity may be involved in the reduction of resting ABP following IHG training. One of the intentions of this study was to quantify the ANS and baroreceptor sensitivity prior to and following an intervention aimed to decrease resting ABP.

4.4 Limitations

There are a variety of factors that may have influenced the results of this study. The first issue is the variability of blood pressure and heart rate over the course of a day and as a result of exogenous stimuli (Pickering, 1998). An attempt to control these variables was made by scheduling appointments at a similar time during the afternoon to account for 24 hour variability. Also, participants were given written guidelines to follow prior to each visit. These guidelines were: no strenuous exercise 24 hours before an appointment, no caffeine or alcohol 12 hours prior to an appointment and no food for 4

hours before a scheduled visit. Although an effort was put forth to control these external stimuli, issues such as fatigue, pain and emotional disturbances are difficult to control.

Another issue that limited this study was the power of our investigation (n=14). The IHG trained group consisted of 8 participants, while there were 6 participants in the control group. The sample size was small due to an assortment of reasons. One issue was the requirements of participants to follow our guidelines and visit our laboratory 12 times over the course of 3 months. Another factor was the inclusion criteria required of participants to qualify for this study. Resting SBP and DBP were required to be above 130 mmHg and/or 85 mmHg respectively, but not high enough to warrant medication for hypertension, which was an exclusion criteria for this investigation.

The fact that the training for this study was home-based is another issue that may have influenced the results, in comparison to previous IHG training studies, which were laboratory-based (Peters et al., 2005; Ray & Carrasso, 2000; Taylor et al., 2003; Wiley et al., 1992). The purpose of this study was to investigate whether IHG training, along with lifestyle modifications, is a suitable therapy for physicians to recommend to non-medicated hypertensives. Participants completed only 2 IHG training sessions under the supervision of an investigator, while the 16 other sessions were home-based. The home-based protocol may be less effective than a supervised protocol. According to certain rehabilitation studies, home-based exercise may not be as beneficial as hospital-based exercise (Karapolat et al., 2007, Patterson et al., 1997 & Regensteiner et al., 1997).

The final factor that may have influenced the results of this investigation is the length of the study. Previous research has utilized a training protocol of 5 to 10 weeks in

length (Peters et al., 2006, Ray & Carrasco, 2000 & Wiley et al., 1992, Taylor et al., 2003). However, in contrast to the present study, the training sessions in these particular studies were supervised by an investigator. Since home-based exercise may not produce the same results as supervised training, it may have been beneficial to increase the length of the present study since the reduction in resting ABP as a result of IHG training has been reported to be proportional to the length of training (Millar et al., 2007).

4.5 Summary

IHG training has been revealed as a potential therapy for the reduction of resting ABP (Peters et al., 2005; Ray & Carrasso, 2000; Taylor et al., 2003; Wiley et al., 1992). Various mechanisms for this reduction in resting ABP with chronic isometric training have been proposed, such as changes in baroreflex sensitivity, the peripheral vasculature, oxidative stress and/or an alteration in the modulation of the ANS (Taylor et al., 2003). Taylor and colleagues (2003) identified a shift in ANS modulation to a larger vagal component and a smaller sympathetic component following IHG training.

The present study was the first to examine handgrip training as a potential intervention for newly diagnosed hypertensive individuals and assess autonomic modulation prior to and after the intervention. Contrary to our hypothesis, 6 weeks of bilateral IHG training in combination with lifestyle modification recommendations, did not result in a reduction of resting ABP or change indices of HRV. Possible explanations for these results are the small sample size of this investigation and the fact that the present study was the first to use home-based training.

4.6 Future Directions

This study could be improved if the power of the investigation was increased by the recruitment of more participants. The length of the training protocol should be raised to 8 or 10 weeks if the study was to continue, in order to allow an ample amount of time for an effect to become evident. Also, a better system for the home-based training needs to be put in place. If the handgrip dynamometer could produce an electronic copy of the results for each session, investigators and physicians would have a better indication of training patterns. Suggestions should be made to the manufacturers regarding a system which would allow the handgrip dynamometer to be hooked up to a computer so that the training session can be recorded and the information can be passed on to a clinician or investigator. This recording system would be superior to the self-reported protocol used in the current study.

An alternative suggestion to increase the effectiveness of the present investigation would be to add a third group of newly diagnosed unmedicated hypertensives who would complete their handgrip training under supervision. If the supervised group reduced their resting ABP to a greater extent than the home-based group, this may be a good indication that recommending IHG training to newly diagnosed hypertensive individuals may not be suited to a home environment.

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5.0 APPENDICES

Appendix A: Consent Form

EXERCISE METABOLISM RESEARCH GROUP
DEPARTMENT OF KINESIOLOGY, MCMASTER UNIVERSITY

INFORMATION & CONSENT TO PARTICIPATE IN RESEARCH

The use of isometric handgrip training to lower blood pressure in family practice medicine

You are being invited to participate in a research study being conducted by the investigators listed below. Before participating in this study you are asked to read this form, which outlines the purpose and testing procedures used in this study. In addition, you are asked to answer some questions regarding your health included in the attached forms (Subject Screening Questionnaire). Unless otherwise stated, all testing and experimental procedures will be conducted in the Exercise and Metabolism Research Lab (Room A103), in the Ivor Wynne Centre at McMaster University. This project is being completed as a Masters level thesis.

INVESTIGATOR:	DEPARTMENT:	CONTACT:
Dr. Neil McCartney	Kinesiology, IWC 210	x24469
Melanie Stuckey	Kinesiology, IWC AB132B	x27384
Amanda Paashuis	Kinesiology, IWC AB131B	x 26086

PURPOSE:

High blood pressure is a risk factor for cardiovascular disease. The current treatments for high blood pressure are medications and exercise. One negative effect of medications is the risk of adverse side effects. This has increased the popularity of exercise for prevention and treatment of hypertension. Isometric handgrip exercise may reduce high blood pressure. The purpose of this study is two-fold: first, to determine the effect of isometric handgrip exercise training on resting blood pressure in people who have just been diagnosed with high blood pressure. Second, this study will examine any possible changes in the body systems controlling blood pressure. These findings may have important implications for the types of exercise recommended to treat high blood pressure.

DESCRIPTION OF TESTING PROCEDURES:

Familiarization and baseline testing (Week 1 and 2): The study will last 9 weeks and we are hoping that 80 people will take part. If you agree to participate in the study you will be randomly chosen to be in either a handgrip or standard treatment group following two weeks of blood pressure measures. This group placement will be random, but based upon resting blood pressure values.

Participants allocated to the standard treatment group will be offered access to handgrip exercise after the study is over.

Handgrip training

Each participant in the handgrip group will be given a digital handgrip device to complete their training. The protocol for training consists of 4 two minute contractions each separated by a 1 minute rest period. The training will involve both hands. You will be training for 3 times each week.

During the first two weeks of the study, you will visit the laboratory three times to allow for familiarization with the laboratory, investigators and testing procedures. These three visits will proceed as follows:

Week 1: Visit 1

- 10 minutes of rest
- 4 blood pressure and heart rate measures
- Health Questionnaire (screening)
- Consent form
- Questionnaires (demographics, trust in physician, self-evaluation, perceived stress)
- Physical Activity Log will be explained
- Measure body weight
- Maximal hand strength test
- Receive a 3 day dietary log (To be completed on 2 weekdays and 1 day on the weekend)

Week 1: Visit 2

- 10 minutes of supine rest
- 4 blood pressure and heart rate measures
- Familiarization with testing protocol and equipment

Week 2: Visit 3

- 10 minutes of supine rest
- 4 blood pressure and heart rate measures
- Hand in dietary log

Participants divided into handgrip and standard treatment groups following Visit 3.

Week 2: Visit 4

All Participants

- 10 minutes of supine rest

- 4 blood pressure and heart rate measures
- Cardiovascular testing (described below)
- Record daily physical activity

Cardiovascular Testing Protocol

1. Heart rate
2. Breathing rate
3. Blood Pressure
4. Tilt testing

Handgrip Group Only

- Discuss and demonstrate technique and procedures for training
- First isometric handgrip training session
- Self-efficacy and exercise intentions questionnaires

Weeks 3 – 8:

Following initial testing the handgrip group will begin the handgrip training (described at the end of this section). During these 6 weeks both groups will follow their doctor's recommendations regarding lifestyle modifications to reduce their blood pressure. All participants in both groups will report to the Ivor Wynne Centre at McMaster University to have their blood pressure monitored once each week.

Week 9 –: Visit 11

All Participants

- 10 minutes of supine rest
- 4 blood pressure and heart rate measures
- Cardiovascular testing (described below)
- Hand in daily physical activity log
- Receive a 3 day dietary log (To be completed on 2 weekdays and 1 day on the weekend)

Cardiovascular Testing Protocol

1. Heart rate
2. Breathing rate
3. Blood Pressure
4. Tilt testing

Week 9: Visit 12

- 10 minutes of supine rest

- 4 blood pressure and heart rate measures
- Questionnaires (self-evaluation, perceived stress)

Visit 13

- 10 minutes of supine rest
- 4 blood pressure and heart rate measures
- Hand in dietary log

Resting Blood Pressure: The blood pressure measurement involves the placement of an inflatable cuff around the upper arm. Blood pressure will also be monitored continuously during the cardiovascular testing using a device which wraps around your middle finger to detect blood pressure in an artery in your finger. There is no risk to this procedure however some individuals experience some discomfort when the cuff is inflated.

Heart Rate: During cardiovascular testing you will be outfitted with 3 electrodes (two placed below each collar bone and the third placed on the left side of your chest below the nipple). The heart rate signal will be recorded electronically. There is no risk to this procedure although sometimes a slight rash can develop from the electrode adhesive.

Respiratory Frequency: During testing you will have a belt wrapped around your chest that will be used to record your breathing rate.

Tilt testing: Heart rate and blood pressure will be measured when you are lying down at rest and also when you are tilted above the horizontal position with a specialized tilt table device. Tilt table testing is designed to evaluate how the body controls blood pressure in response to some very simple stresses. The test will begin with you lying flat on your back on the tilt table for 30 minutes with your feet supported on a platform. Then you will be tilted to 40 degrees for 10 minutes, which feels like lying on a steep hill. During the last 10 minutes of the test you will be tilted to 60 degrees. You will have safety straps around your waist and knees at all times to make you feel secure. Heart rate and blood pressure will be monitored continuously and you will control your breathing rate during this procedure. You may begin to feel dizzy when tilted upright similar to when you stand up quickly or stand in one position for a long time. If this happens the test will be ended.

Arterial Compliance: While you are lying down, one of the investigators will measure the pressure in the artery in your neck with a pen-like device. It will feel like the flat end of a pen pressing gently over the pulse in your neck. There are no risks to this procedure, however some people feel some discomfort from the pressure of the device.

POTENTIAL RISKS AND DISCOMFORTS:

The isometric handgrip exercise itself may cause some physical discomfort. Although none of the participants in the research carried out thus far have experienced injury from isometric exercise using the handgrip device, you could experience muscle soreness as a consequence of the training.

BENEFITS & REMUNERATION:

In participating in this project you realize that there are no direct benefits to you. Benefits to the participant include consistent monitoring of weekly blood pressures and the potential to lower resting blood pressure. The benefits to society include further evidence on the relationship between blood pressure and isometric exercise.

For participating in this study you will receive remuneration for all parking incurred through this study. All parking costs will be covered if you choose to withdraw from this study.

CONFIDENTIALITY:

All data collected during this study will remain confidential and stored in offices and on computers to which only the investigator has access. You should be aware that the results of this study will be made available to the scientific community, through publication in a scientific journal, although neither your name nor any reference to you will be used in compiling or publishing these results. Additionally, you will have access to your own data, as well as the group data when it becomes available and if you're interested. You are asked to contact the investigators by phone or email to obtain results following an adequate period for analysis, if you so wish.

PARTICIPATION & WITHDRAWL

Your participation in this study is entirely voluntary. You can choose whether to participate in this study or not. You can drop out of the study at any time, even after the testing has started, with no consequence. Any data you have provided to that point will be destroyed, unless you indicate otherwise. You also have the right to refuse to answer any question posed to you during the study and still remain as a subject in the study. The investigators reserve the right to withdraw you from the study if they believe that circumstances have arisen which warrant doing so.

Costs

Taking part in this research project will not involve any costs to you.

RIGHTS OF RESEARCH PARTICIPANTS

You will receive a signed copy of this ethics form. You may withdraw your consent to participate in this study at any time, and you may also discontinue participation at any time without penalty. In signing this consent form or in participating in this study you are not waiving any legal claims or remedies. This study has been reviewed and received clearance from the Hamilton Health Sciences Research Ethics Board and St. Joseph's Healthcare Research Ethics Board. If you have any further questions regarding your rights as a research participant contact:

REB Secretariat, CNH-111
McMaster University
1280 Main St. W.
Hamilton, ON
L8S 4L9

Tel: (905) 525-9140 x24765
Fax: (905) 540-8019
Email: grntoff@mcmaster.ca

OR

You may also contact the Hamilton Health Sciences Patient Relations Specialist at 905-521-2100, Ext. 75240

INFORMATION:

You will be able to contact
Melanie Stuckey, Hon. B.Sc. at 525-9140 (x27384) or stuckemi@mcmaster.ca
Amanda Paashuis, Hon. B. Sc. & BPHE at 525-9140 (x26086) or paashuaa@mcmaster.ca
Neil McCartney Ph.D. at 525-9140 (x24469) or mccartne@mcmaster.ca
regarding any questions about this portion of the study.

I HAVE READ AND UNDERSTAND THE ABOVE EXPLANATION OF THE PURPOSE AND PROCEDURES OF THE PROJECT. I HAVE ALSO READ AND COMPLETED THE ATTACHED FORM ENTITLED "SUBJECT SCREENING QUESTIONNAIRE" AND AGREE TO PARTICIPATE AS A SUBJECT. I WILL ALSO RECEIVE A SIGNED COPY OF THE INFORMATION AND CONSENT FORM. MY QUESTIONS HAVE BEEN ANSWERED TO MY SATISFACTION AND I AGREE TO PARTICIPATE IN THIS STUDY.

_____ _____

SIGNATURE DATE

_____ _____

PRINTED NAME OF PARTICIPANT DATE

_____ _____

WITNESS DATE

_____

PRINTED NAME OF WITNESS

INVESTIGATOR

In my judgement the participant in voluntarily and knowingly giving informed consent and possesses the legal capacity to give informed consent and participate in this research study.

_____ _____

SIGNATURE OF INVESTIGATOR DATE

_____

PRINTED NAME OF INVESTIGATOR

☐ Check box if you would like to be considered for future research projects

Appendix B – Medical Questionnaire

METABOLISM RESEARCH GROUP
DEPARTMENT OF KINESIOLOGY, MCMASTER UNIVERSITY

SUBJECT SCREENING QUESTIONNAIRE

Your responses to this questionnaire are confidential and you are asked to complete it for your own health and safety. Your responses will ensure that all participants meet the inclusion/exclusion criteria for this study. They will also enable us to more accurately assess your ability to partake in the exercise protocol.

If you answer "YES" to any of the following questions, please give additional details in the space provided and discuss the matter with one of the investigators. You may refuse to answer any of the following questions.

Code: _____ Date: _____

1. Have you ever been told that you have a heart problem?

   YES NO

If yes – please explain:

2. Have you smoked in the last 5 years?

   YES NO

3. Have you ever been told that you have diabetes?

   YES NO

If yes – please explain:

4. Have you ever had any major joint instability or ongoing chronic pain such as in the knee, back or elbow?

   YES NO

If yes – please explain:

5. Are you currently undergoing Hormone Replacement Therapy (HRT)?

   YES NO

6. Have you had any allergies to medication?

YES NO

If yes – please explain:

7. Have you had any allergies to food or environmental factors?

YES NO

If yes – please explain:

8. Do you have a hard time walking great distances? (>400m)

YES NO

If yes – please explain (symptoms, severity):

9. When you receive a blow to a muscle do you develop bruises easily?

YES NO

10. Are you currently taking any medication (including aspirin) or have you taken any medication in the last two days?

YES NO

If yes – please explain:

11. Is there any medical condition with which you have been diagnosed and are under the care of a physician (e.g. diabetes, high blood pressure)?

YES NO

If yes – please explain:

ANY ADDITIONAL COMMENTS:

Appendix C – Leisure Time Physical Activity Questionnaire

How active have you been over the past six weeks?

MODERATE Physical Activity Definition
Moderate physical activity or exercise includes activities such as brisk walking, light swimming, dancing, biking, gardening, and yardwork. You should be able to carry on a conversation when doing moderate activities. Please consider a TYPICAL week for you and answer the following questions about moderate activities.

1. During the past 6 weeks, how many days per week did you engage in moderate physical activity? _____ **days per week**

2. Approximately how many minutes did you engage in moderate physical activity each day? _____ **minutes per day**

VIGOROUS Physical Activity Definition:
Vigorous physical activity or exercise includes hard activities such as jogging, aerobics, swimming, and fast biking. You may have a hard time carrying on a conversation when doing vigorous activities. Please consider a TYPICAL week for you and answer the following questions about vigorous activities.

1. During the past 6 weeks, how many days per week did you engage in vigorous physical activity? _____ **days per week**

2. Approximately how many minutes did you engage in vigorous physical activity each day? _____ **minutes per day**

Appendix D – Handgrip Training and Physical Activity Log Sheet

Participant Number: ☐ Dates of Record: ☐

Please record the results for your **handgrip training AND** your **participation in leisure time physical activity** during each day.

Strenuous (Stren) Exercise = Heart beats rapidly with large increases in breathing
Moderate (Mod) Exercise = Not exhausting with small increases in breathing or heart rate
Mild (Mild) Exercise = Minimal Effort (i.e. easy walking)
Example:

Day	Handgrip Training	Activity	Intensity (circle one)	Duration (mins.)
Monday	Max. Force: 68 Score: 92	Fast walking to park and back	Stren/(Mod)/Mild	30

Day	Handgrip Training	Activity	Intensity (circle one)	Duration (mins.)
Monday	Max. Force: ____ Score: ___		Stren/Mod/Mild	
			Stren/Mod/Mild	
			Stren/Mod/Mild	
Tuesday			Stren/Mod/Mild	
			Stren/Mod/Mild	
			Stren/Mod/Mild	
Wednesday	Max. Force: ____ Score: ___		Stren/Mod/Mild	
			Stren/Mod/Mild	
			Stren/Mod/Mild	
Thursday			Stren/Mod/Mild	
			Stren/Mod/Mild	
			Stren/Mod/Mild	
Friday	Max. Force: ____ Score: ___		Stren/Mod/Mild	
			Stren/Mod/Mild	
			Stren/Mod/Mild	

Appendix E - Study Data

Participant Characteristics

Participant #	Training Subjects	Sex	Age	BMI	Baseline SBP	Baseline DBP
1	JM	M	32	25	128	78
4	WR	M	67	25	144	75
5	BN	F	63	24	147	76
7	SA	M	47	29	144	96
8	KM	F	59	20	163	80
11	NT	F	49	26	125	79
12	DL	F	45	24	132	81
13	PW	M	55	28	141	93
Mean			52.1	25.0	140.3	82.4
SEM			4.0	1.0	4.3	2.8

Participant #	Control Subjects	Sex	Age	BMI	Baseline SBP	Baseline DBP
3	EM	F	62	30	144	99
6	RC	M	70	47	152	77
9	LS	F	58	34	127	73
10	LM	F	41	23	136	82
14	CB	F	57	33	141	82
15	MB	M	42	21	130	82
Mean			55.0	31.2	138.2	82.3
SEM			4.7	3.8	3.8	4.4

Sex: M = Male, F = Female
Age: Represented in years
Baseline SBP: SBP = Systolic Blood Pressure
Baseline DBP: DBP = Diastolic Blood Pressure (SBP and DBP represented in mmHG)
SEM = standard error of the mean

Systolic Blood Pressure Data

Training Group

Participant	Pre1	Pre2	Pre3	AVGPre	Week 1	Week 2	Week 3	Week 4	Week 5	Post 1	Post 2	Post 3	AVGPost
1	131.0	125.5	126.5	127.7	125.0	126.0	123.0	121.5	121.5	121.0	123.0	123.0	122.3
3	141.5	143.5	146.0	143.7	160.5	159.5	150.0	150.0	148.5	152.5	152.5	152.5	152.5
5	147.0	141.0	152.5	146.8	152.5	150.0	141.5	131.5	141.5	148.0	128.0	142.5	139.5
7	150.5	133.0	149.0	144.2	151.0	145.0	148.5	152.0	144.0	153.0	148.5	147.5	149.7
8	172.5	167.5	149.5	163.2	143.5	143.0	152.5	156.0	145.5	159.0	144.0	134.5	145.8
11	132.0	119.0	124.5	125.2	124.0	123.5	129.5	133.5	125.0	134.5	131.5		133.0
12	133.5	129.0	132.5	131.7	134.5	128.5	133.0	138.0	134.0	132.0	135.0	133.5	133.5
13	144.0	143.5	134.0	140.5	142.5	150.5	149.5	151.5	147.0	150.0	146.5	151.5	149.3
MEAN	144.0	137.8	139.3	140.4	141.7	140.8	140.9	141.8	138.4	143.8	138.6	140.7	140.7
SEM	4.8	5.3	4.0	4.3	4.6	4.7	3.9	4.4	3.7	4.6	3.8	4.1	3.7

Control Group

Participant	Pre1	Pre2	Pre3	AVGPre	Week 1	Week 2	Week 3	Week 4	Week 5	Post 1	Post 2	Post 3	AVGPost
4	145.0	137.0	148.5	143.5	150.0	160.0	146.0	148.5	154.5	143.0	150.5	152.5	148.7
6	155.5	146.0	154.0	151.8	149.5	153.5	135.5	138.5	144.0	141.0	155.5	156.0	150.8
9	134.0	132.0	113.5	126.5	123.5	120.0	123.0	117.5	109.0	124.0	115.0	117.5	118.8
10	136.5	135.5	136.0	136.0	124.5	120.5	123.5	122.5	131.0	127.5	130.0	126.0	127.8
14	150.5	141.5	131.5	141.2			140.0	140.0	140.0	133.0	142.5	133.5	136.3
15	131.5	126.5	132.5	130.2	126.5	126.5	124.5	124.0		130.0	129.0	126.5	128.5
MEAN	142.2	136.4	136.0	138.2	134.8	136.1	132.1	131.8	135.7	133.1	137.1	135.3	135.2
SEM	3.9	2.8	5.8	3.8	6.1	8.6	4.0	5.0	7.7	3.1	6.2	6.3	5.1

All data are represented as mmHg and are an average of supine and seated measurements
SEM = standard error of the mean

Diastolic Blood Pressure Data

Training Group

Participant	Pre1	Pre2	Pre3	AVGPre	Week 1	Week 2	Week 3	Week 4	Week 5	Post 1	Post 2	Post 3	AVGPost
1	79.0	76.0	80.0	78.3	78.0	74.0	79.0	78.0	76.5	76.5	80.5	81.0	79.3
3	78.0	73.5	74.0	75.2	85.0	84.5	80.0	79.5	79.5	83.0	80.5	82.0	81.8
5	76.5	76.5	75.0	76.0	81.0	81.5	76.5	70.5	81.5	84.0	69.0	82.0	78.3
7	98.5	91.5	99.0	96.3	96.5	91.5	95.0	103.0	89.0	99.5	95.5	93.5	96.2
8	78.5	79.5	82.0	80.0	70.5	72.5	75.5	78.0	75.0	78.5	71.5	73.0	74.3
11	85.0	76.5	76.5	79.3	76.0	79.5	84.0	85.0	81.5	88.5	86.5		87.5
12	82.5	77.5	83.5	81.2	83.0	82.0	82.0	82.0	84.5	83.0	83.0	80.5	82.2
13	97.5	93.5	87.5	92.8	86.0	94.5	97.5	99.5	97.0	96.5	97.0	96.5	96.7
MEAN	84.4	80.6	82.2	82.4	82.0	82.5	83.7	84.4	83.1	86.2	82.9	84.1	84.5
SEM	3.1	2.7	2.9	2.8	2.7	2.7	2.9	4.0	2.5	2.9	3.5	3.1	2.9

Control Group

Participant	Pre1	Pre2	Pre3	AVGPre	Week 1	Week 2	Week 3	Week 4	Week 5	Post 1	Post 2	Post 3	AVGPost
4	100.0	93.0	102.5	98.5	104.0	109.0	99.5	104.0	105.5	98.0	101.5	104.0	101.2
6	79.5	76.0	74.5	76.7	81.5	80.0	70.0	72.0	73.0	72.5	76.0	78.5	75.7
9	74.5	73.5	70.5	72.8	68.5	68.5	71.5	69.0	66.0	68.0	70.0	71.5	69.8
10	81.0	79.0	85.0	81.7	77.5	75.0	78.0	77.5	77.0	78.5	78.5	75.5	77.5
14	85.0	82.5	79.0	82.2			83.5	82.5	81.5	81.0	84.0	78.5	81.2
15	82.5	79.5	83.5	81.8	80.0	75.5	81.0	83.5		81.5	79.5	81.0	80.7
MEAN	83.8	80.6	82.5	82.3	82.3	81.6	80.6	81.4	80.6	79.9	81.6	81.5	81.0
SEM	3.6	2.8	4.6	3.6	5.9	7.1	4.4	5.1	6.7	4.2	4.4	4.7	4.4

All data are represented as mmHg and are an average of supine and seated measurements
SEM = standard error of the mean

Mean Arterial Blood Pressure Data

Training Group

Participant	Pre1	Pre2	Pre3	AVGPre	Week 1	Week 2	Week 3	Week 4	Week 5	Post 1	Post 2	Post 3	AVGPost
1	97.0	94.0	95.5	95.5	95.5	92.5	94.5	92.5	91.5	91.5	95.0	95.0	93.8
3	101.0	99.5	101.0	100.5	112.0	112.5	105.5	106.0	106.0	109.0	106.5	107.5	107.7
5	101.0	101.0	103.5	101.8	108.5	107.0	99.0	93.0	104.5	101.0	95.5	104.5	100.3
7	121.0	105.5	116.5	114.3	117.0	111.0	114.5	120.0	108.0	118.5	114.5	113.0	115.3
8	113.0	112.5	107.0	110.8	97.0	98.0	104.5	107.5	100.0	109.0	99.0	94.5	100.8
11	102.0	91.0	93.0	95.3	93.5	94.5	99.5	101.0	96.5	104.5	102.0		103.3
12	100.5	96.0	100.5	99.0	101.0	97.5	100.0	101.5	101.5	100.0	101.0	99.0	100.0
13	114.5	110.5	103.5	109.5	109.0	114.5	115.0	118.5	112.5	115.5	114.0	117.5	115.7
MEAN	106.3	101.3	102.6	103.4	104.2	103.4	104.1	105.0	102.6	106.1	103.4	104.4	104.6
SEM	3.1	2.7	2.5	2.6	3.0	3.1	2.6	3.6	2.4	3.1	2.7	3.3	2.7

Control Group

Participant	Pre1	Pre2	Pre3	AVGPre	Week 1	Week 2	Week 3	Week 4	Week 5	Post 1	Post 2	Post 3	AVGPost
4	109.0	118.5	117.0	114.8	128.0	116.0	119.0	123.0	112.5	118.0	122.0	113.0	117.7
6	107.5	102.0	105.0	104.8	104.5	107.0	93.5	97.0	99.0	98.0	106.0	108.0	104.0
9	96.5	94.5	87.0	92.7	90.0	88.5	90.5	88.0	84.5	89.0	87.5	88.5	88.3
10	102.0	99.5	102.5	101.3	94.5	90.5	93.5	93.0	96.0	95.0	96.5	90.0	93.8
14	109.0	103.0	98.5	103.5			103.0	102.5	103.0	99.5	105.5	98.0	101.0
15	100.5	95.0	99.5	98.3	96.5	93.5	95.0	97.0		97.0	96.5	97.5	97.0
MEAN	104.1	102.1	101.6	102.6	102.7	99.1	99.1	100.1	99.0	99.4	102.3	99.2	100.3
SEM	2.1	3.6	4.0	3.0	6.7	5.3	4.3	5.0	4.6	4.0	4.8	4.0	4.1

All data are represented as mmHg and are an average of supine and seated measurements
SEM = standard error of the mean

Heart Rate Data

Training Group

Participant	Pre1	Pre2	Pre3	AVGPre	Week 1	Week 2	Week 3	Week 4	Week 5	Post 1	Post 2	Post 3	AVGPost
1	69.0	60.5	58.5	62.7	61.5	57.5	53.5	60.5	59.5	59.5	60.0	60.5	60.0
3	53.5	49.5	50.5	51.2	53.5	55.0	56.5	60.5	56.5	54.5	51.5	54.5	53.5
5	65.5	65.0	62.5	64.3	65.5	63.0	67.0	70.5	64.0	67.0	62.0	60.0	63.0
7	62.5	65.0	68.0	65.2	60.5	62.0	64.5	64.5	65.0	56.0	58.0	66.0	60.0
8	59.0	60.5	64.0	61.2	59.5	59.0	59.5	60.0	73.0	55.5	57.5	67.0	60.0
11	87.0	91.0	79.0	85.7	85.5	87.0	93.0	97.0	94.0	80.5	85.5		83.0
12	84.0	79.5	82.5	82.0	77.5	78.0	74.5	77.5	76.5	83.0	75.0	79.0	79.0
13	58.0	58.5	62.0	59.5	58.5	62.5	60.5	56.0	60.5	60.0	59.0	59.5	59.5
MEAN	67.3	66.2	65.9	66.5	65.3	65.5	66.1	68.3	68.6	64.5	63.6	63.8	64.8
SEM	4.3	4.6	3.7	4.1	3.8	3.9	4.5	4.8	4.3	4.0	3.9	3.0	3.7

Control Group

Participant	Pre1	Pre2	Pre3	AVGPre	Week 1	Week 2	Week 3	Week 4	Week 5	Post 1	Post 2	Post 3	AVGPost
4	74.5	77.5	79.5	77.2	73.0	77.0	78.5	79.5	85.5	73.0	78.0	77.5	76.2
6	57.0	61.0	60.0	59.3	54.0	54.0	55.0	61.0	59.0	55.5	55.5	51.0	54.0
9	83.5	79.0	79.0	80.5	71.5	75.0	75.0	71.5	73.5	74.5	67.0	79.5	73.7
10	75.0	66.5	67.0	69.5	69.5	66.0	63.0	64.5	65.5	72.5	64.5	73.0	70.0
14	76.0	65.5	67.0	69.5			66.0	66.5	69.5	66.0	62.5	60.5	63.0
15	65.0	65.5	71.5	67.3	58.0	60.0	53.5	55.5		82.5	63.5	61.0	69.0
MEAN	71.8	69.2	70.7	70.6	65.2	66.4	65.2	66.4	70.6	70.7	65.2	67.1	67.6
SEM	3.8	3.0	3.1	3.1	3.8	4.4	4.2	3.4	4.4	3.7	3.0	4.6	3.3

SEM = standard error of the mean
All data are represented as beats per minute and are an average of supine and seated measurements

Heart Rate Variability Data at Rest

Participant	Group	%LFA Pre	%LFA Post	%HFA Pre	%HFA Post	LFA Pre	LFA Post	HFA Pre	HFA Post	LF:HF Pre	LF:HF Post
1	2	40.4	40.2	59.6	59.8	101.8	100.8	150.1	149.7	0.7	0.7
4	2	69.1	74.9	30.9	25.1	174.4	189.6	78.0	63.4	2.2	3.0
5	2	59.7	52.8	40.3	47.2	150.9	133.6	101.7	119.6	1.5	1.1
7	2	74.6	77.7	25.4	22.3	188.8	196.7	64.4	56.6	2.9	3.5
8	2	54.4	70.5	45.6	29.5	135.2	178.7	113.4	74.7	1.2	2.4
11	2	50.8	39.0	49.2	61.0	127.6	98.0	123.5	153.3	1.0	0.6
12	2	61.6	59.5	38.4	40.5	155.0	150.1	96.6	102.0	1.6	1.5
13	2	88.1	87.5	11.9	12.5	224.8	222.6	30.3	31.8	7.4	7.0
3	1	67.1	70.5	32.9	29.5	163.3	174.9	80.1	73.3	2.0	2.4
9	1	64.3	54.6	35.7	45.4	162.4	137.6	90.0	114.2	1.8	1.2
10	1	23.7	21.4	76.3	78.6	59.3	53.0	191.2	194.1	0.3	0.3
14	1	64.6	39.1	35.4	60.9	163.8	98.2	89.6	153.1	1.8	0.6
15	1	80.0	87.7	20.0	12.3	202.7	223.5	50.7	31.3	4.0	7.1

Units for LFA and HFA are represented as $(beats/min)^2/Hz$

Heart Variability Data During Passive Tilt

Participant	Group	%LFA Pre	%LFA Post	%HFA Pre	%HFA Post	LFA Pre	LFA Post	HFA Pre	HFA Post	LF:HF Pre	LF:HF Post
1	2	85.4	90.6	14.6	9.4	217.3	231.3	37.2	24.1	5.8	9.6
4	2	78.7	81.6	21.3	18.4	198.9	206.0	54.0	46.5	3.7	4.4
5	2	87.1	80.0	12.9	20.0	221.6	202.9	32.8	50.8	6.8	4.0
7	2	81.3	87.3	18.7	12.7	206.3	223.1	47.4	32.3	4.3	6.9
8	2	91.5	92.0	8.5	8.0	232.7	235.0	21.7	20.3	10.7	11.6
11	2	44.3	46.0	55.7	54.0	110.8	114.7	139.3	134.9	0.8	0.9
12	2	47.7	49.4	52.3	50.6	120.7	125.2	132.6	128.3	0.9	1.0
13	2	91.5	89.4	8.5	10.6	233.3	228.1	21.8	26.9	10.7	8.5
3	1	90.1	86.4	9.9	13.6	227.3	217.8	25.1	34.3	9.1	6.3
9	1	92.1	86.4	7.9	13.6	233.6	219.9	20.0	34.6	11.7	6.4
10	1	23.2	42.3	76.8	57.7	56.2	102.3	186.5	139.3	0.3	0.7
14	1	69.0	83.0	31.0	17.0	176.9	208.9	78.6	42.7	2.2	4.9
15	1	80.0	62.1	20.0	37.9	202.7	157.7	50.7	39.7	4.0	1.6

Units for LFA and HFA are $(beats/min)^2/Hz$

Kilocalories, Sodium Intake, Total Body Weight and Physical Activity

Participant	Group	Kilocalories Pre	Kilocalories Post	Sodium (mg) Pre	Sodium (mg) Post	Weight (kg) Pre	Weight (kg) Post	Activity (min) Pre	Activity (min) Post
1	2	1810.4	2067.5	1441.4	3090.4	89.5	89.1	135.0	110.0
4	2	1169.0	1236.0	1582.7	2031.7	66.0	68.0	225.0	225.0
5	2	1717.0	1377.9	2770.9	1295.1	66.2	65.5	180.0	120.0
7	2	1830.7	2033.4	1366.4	1414.8	93.0	93.9	300.0	260.0
8	2	1695.5	2220.5	2443.0	3479.6	56.0	55.2	240.0	260.0
11	2	1374.7	1423.1	1151.4	1181.0	66.7	68.0	150.0	420.0
12	2	1622.3	1626.3	3446.6	2265.2	68.0	66.8	150.0	180.0
13	2					83.0	83.7	135.0	285.0
3	1	1128.6	1234.3	1348.9	2445.3	71.4	74.5	0.0	120.0
6	1	1860.2	1660.8	3859.8	2524.6	137.5	135.5	0.0	0.0
9	1	1335.2	1105.6	1846.0	1193.1	85.3	83.5	280.0	360.0
10	1	2134.3	1592.3	2196.8	1899.9	70.1	66.5	180.0	150.0
14	1	1835.2	1339.7	2168.3	1641.9	86.2	81.6	120.0	180.0
15	1	1752.3	1932.7	2606.2	2982.2	62.6	62.1	140.0	248.0

Appendix F – ANOVA Summary Tables

Absolute Systolic Blood Pressure

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	101.676666	12	222.503128	0.4569	0.51186281
Time (T)	1	12.254	12	31.5413	0.3885	0.544749
G x T	1	19.6072	12	31.5413	0.6216	0.44573686

Marked Effects at p<0.05

Absolute Diastolic Blood Pressure

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	22.9604	12	148.5083	0.1546	0.70106739
Time (T)	1	1.2917	12	6.4840	0.1992	0.66329885
G x T	1	20.0933	12	6.4840	3.0989	0.10378506

Marked Effects at p<0.05

Absolute Mean Arterial Blood Pressure

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	44.2371	12	118.3476	0.3738	0.55235195
Time (T)	1	1.7743	12	12.7929	0.1387	0.71607459
G x T	1	21.4608	12	12.7929	1.6776	0.21961263

Marked Effects at p<0.05

Heart Rate

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	83.6670	12	187.8939	0.4453	0.517208
Time (T)	**1**	**36.6696**	**12**	**4.3970**	**8.3397**	**0.013630**
G x T	1	2.5030	12	4.3970	0.5692	0.465107

Marked Effects at p<0.05

Heart Rate Variability %HF Area Supine

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	161.9461	11	703.6110	0.2302	0.64079922
Time (T)	1	32.8340	11	55.0303	0.5967	0.45613414
G x T	1	45.9274	11	55.0303	0.8346	0.38053831

Marked Effects at p<0.05

Heart Rate Variability %LF Area Supine

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	161.9505	11	703.6129	0.2302	0.64079529
Time (T)	1	32.8359	11	55.0297	0.5967	0.45611891
G x T	1	45.9251	11	55.0297	0.8346	0.38054764

Marked Effects at p<0.05

Heart Rate Variability HF Area Supine

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	909.249939	11	4375.5693	0.2078	0.65736365
Time (T)	1	201.608521	11	337.2201	0.5979	0.4556925
G x T	1	265.15683	11	337.2201	0.7863	0.39419442

Marked Effects at p<0.05

Heart Rate Variability LF Area Supine

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	1179.4285	11	4577.6167	0.2577	0.621761
Time (T)	1	178.8529	11	376.8071	0.4747	0.505126
G x T	1	288.4212	11	376.8071	0.7654	0.400333

Marked Effects at p<0.05

Heart Rate Variability LF:HF Area Supine

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	0.1344	11	9.2712	0.0145	0.906347
Time (T)	1	0.6508	11	0.8730	0.7455	0.406352
G x T	1	0.1964	11	0.8730	0.2250	0.644555

Marked Effects at p<0.05

Heart Rate Variability %HF Area During Passive Tilt

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	47.7934	11	846.7327	0.0564	0.81657362
Time (T)	1	70.4209	11	26.9793	2.6102	0.134472683
G x T	1	31.4484	11	26.9793	1.1656	0.303401232

Marked Effects at p<0.05

Heart Rate Variability %LF Area During Passive Tilt

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	191.4023	11	682.3871	0.2805	0.606904149
Time (T)	1	46.7734	11	50.0954	0.9337	0.354670972
G x T	1	62.1835	11	50.0954	1.2413	0.28897211

Marked Effects at p<0.05

Heart Rate Variability HF Area During Passive Tilt

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	201.552444	11	5099.9775	0.0395	0.846048236
Time (T)	1	439.519073	11	169.6264	2.5911	0.135764584
G x T	1	193.17041	11	169.6264	1.1388	0.308767289

Marked Effects at p<0.05

Heart Rate Variability LF Area During Passive Tilt

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	153.3313	11	5856.4370	0.0262	0.874391258
Time (T)	1	156.9286	11	201.6761	0.7781	0.39658308
G x T	1	24.1616	11	201.6761	0.1198	0.735776961

Marked Effects at p<0.05

Heart Rate Variability LF:HF Area During Passive Tilt

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	0.2265	11	27.6736	0.0082	0.929533839
Time (T)	1	5.1497	11	4.0665	1.2664	0.284404129
G x T	1	10.3278	11	4.0665	2.5397	0.139322355

Marked Effects at p<0.05

Average Calorie Intake

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	42954.2422	11	182156.8125	0.2358	0.636777
Time (T)	1	12343.8652	11	39288.2891	0.3142	0.586357
G x T	1	151285.1719	11	39288.2891	3.8506	0.075517

Marked Effects at $p<0.05$

Total Body Weight

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	840.4565	12	805.0716	1.0440	0.327061
Time (T)	1	3.0292	12	1.9094	1.5864	0.231785
G x T	1	5.4685	12	1.9094	2.8639	0.116365

Marked Effects at $p<0.05$

Average Sodium Intake

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	160279.2500	11	872246.4375	0.1838	0.676440
Time (T)	1	33410.0391	11	506698.1250	0.0659	0.802087
G x T	1	147811.1563	11	506698.1250	0.2917	0.599888

Marked Effects at $p<0.05$

Leisure Time Physical Activity

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	27018.3594	12	14544.1758	1.8577	0.197922
Time (T)	1	16957.6465	12	4398.7588	3.8551	0.073192
G x T	1	299.0744	12	4398.7588	0.0680	0.798706

Marked Effects at $p<0.05$