EFFECTS OF ISOMETRIC HANDGRIP TRAINING ON RESTING BLOOD PRESSURE, HEART RATE VARIABILITY AND BLOOD PRESSURE VARIABILITY IN OLDER ADULTS WITH HYPERTENSION

EFFECTS OF ISOMETRIC HANDGRIP TRAINING ON RESTING BLOOD PRESSURE, HEART RATE VARIABILITY AND BLOOD PRESSURE VARIABILITY IN OLDER ADULTS WITH HYPERTENSION

By

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A Thesis

Submitted to the School of Graduate Studies

In Partial Fulfillment of the Requirements

for the Degree

Master of Science

McMaster University

MASTER OF SCIENCE (1999) (Kinesiology)	McMaster University Hamilton, Ontario
TITLE:	Effects of Isometric Handgrip Training on Resting Blood Pressure, Heart Rate Variability and Blood Pressure Variability in Older Adults with Hypertension
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SUPERVISORY COMMITTEE:	Dr. Markad V. Kamath, Ph.D. Dr. Ron Wiley, Ph.D.
NUMBER OF PAGES:	X, 158

ABSTRACT

This study examined the effects of isometric handgrip (IHG) training on resting blood pressure (RBP), heart rate variability (HRV) and blood pressure variability (BPV) in older adults with hypertension. Nine subjects performed four 2-minute IHG contractions at 30% maximal voluntary contraction (MVC) 3 days/week for 10 weeks and 8 subjects served as controls. Power spectral analysis (PSA) of HRV and BPV was used to assess changes in modulation of the autonomic nervous system. After training, there was a marked attenuation in arterial pressure and evidence for a shift in HRV and BPV sympathovagal balance. There was a reduction in systolic blood pressure (156 ± 9.4 to 137 ± 7.8 mm Hg; $p<0.05$), diastolic blood pressure (82 ± 9.3 to 75 ± 10.9 mm Hg; N.S), mean arterial pressure (107 ± 8.53 to 96 ± 8.7 mm Hg; $p<0.05$) and resting heart rate (RHR) (70 ± 14.2 to 68 ± 12.1 beats/min). In addition, PSA of HRV showed a decrease in sympathetic modulation represented by low frequency (LF) area, an increase in parasympathetic modulation represented by high frequency (HF) area ($p<0.05$) and a decrease in LF:HF area ratio. After training, BPV PSA showed a decrease in systolic blood pressure LF area ($p<0.05$), an increase in HF area ($p<0.05$) and decrease in LF:HF area ($p<0.05$). Similar, but non-significant changes occurred in diastolic BPV. It is concluded that isometric training at a moderate intensity can elicit a hypotensive response and can potentially alter sympathovagal balance of HRV and BPV in older adults with hypertension.

This thesis is dedicated to my Mother and to my Grandmother,

Who have allowed me to fulfill all of my dreams and aspirations. Without their love, encouragement and support, the success I have achieved in all of my endeavors would not have been possible.

And to Themios,

Who has
provided me with love and understanding,
helped to strengthen my character,
given me endless encouragement and support,
And who
continues to inspire me.

ACKNOWLEDGEMENTS

"Perseverance is not a long race;
it is many short races one after another."
--Walter Elliott

"The one who says it can't be done
is generally passed by someone doing it"
--Anonymous

I would like to thank those individuals who have it made it possible for me to complete this great milestone. My supervisor Dr. Neil McCartney, who believed in me and in my abilities by giving me the opportunity to pursue this degree and who provided me with ongoing guidance and encouragement.

I would like to acknowledge Dr. Marked Kamath for the endless patience and time he committed to teaching me about PSA, the task was certainly a challenging one. Also, thank you to Dr. Ron Wiley, who inspired and enlightened me. His enthusiasm and vested interest in my research was very motivating. I would like to thank John Moroz for his technical expertise.

I would like to thank the Mac Seniors, without whom my project would not have been possible. And to Karen Winegard, who has become a great friend. Thank you for your friendship, your encouragement and for the great time I had working with you and the Mac Seniors.

Thank you to my classmates, who made my experience as a graduate student a pleasant and memorable one. I truly cherish the friendships I have made.

Finally, to my family and friends who have been so supportive along the way and have been there to pick me up during the tough times. I would especially like to thank Maureen, Gord, Steve and the rest of my running friends for their encouragement, advice and never-ending belief in me.

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1.0 REVIEW OF THE LITERATURE AND STATEMENT OF PURPOSE

1.1 Introduction

Hypertension is often an asymptomatic condition that is characterized by a persistent elevation in arterial blood pressure (Kaplan, 1997; Mohrman, 1997). The definition of hypertension is somewhat arbitrary, with no clearly defined threshold for potential complications related to cardiovascular disease. However, in recent years, attempts have been made to classify the disease into distinct categories for clinical, diagnostic and treatment purposes. The Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure has classified hypertension into four stages: Stage 1 to represent mild hypertension (140-159/90-99 mm Hg); Stage 2 to represent moderate hypertension (160-179/100-109 mm Hg); Stage 3 to represent severe hypertension (180-209/ 110-119 mm Hg); and Stage 4 to represent very severe hypertension (>210/>120 mm Hg) (JNC, 1993). In addition, isolated systolic hypertension, commonly seen in elderly individuals, was defined as a systolic blood pressure of 140 mm Hg or more and a diastolic blood pressure of less than 90 mm Hg.

The term essential hypertension is used to identify cases where elevated blood pressure is of unknown origin, otherwise referred to as primary hypertension (Braunwald, 1997; Mohrman, 1997). When hypertension results from a known cause such as renal disease, endocrine dysfunction, neurological disorders, obesity, familial history, alcohol or drug use, it is referred to as secondary hypertension (Braunwald, 1997; Mohrman, 1997).

The prevalence of hypertension in a given population is dependent on the criteria used in its diagnosis. With the definition of hypertension as a mean blood pressure of 140/90 mm Hg or higher, there is a tendency for the frequency of hypertension to be elevated with increasing age. In the United States, statistics from the National Health and Nutrition Examination Surveys from 1988 to 1991 (NHANES III) revealed that hypertension was most prevalent in older adults (65 to 74 years), affecting approximately 60% of the population (RPPH, 1993). Horan and Mockrin (1990) have previously described hypertension as "a serious public health problem." It has been estimated that about 20% of the adult population in the Western world is affected by hypertension, yet in about 90% of hypertensive cases, no single identifiable cause is known (Mohrman, 1997).

Complications associated with hypertension are dependent on the extent of blood pressure elevation. For instance, manifestation of various cardiovascular diseases through acceleration of atherosclerosis would likely occur with a higher level of blood pressure. Often, the deleterious effects of hypertension are underestimated, since cardiovascular complications are frequently attributed to the end result (e.g. myocardial infarction or stroke) rather then to the underlying etiology responsible for initiating the vascular damage. A potential precursor to hypertension is an increase in left ventricular wall tension. The increased wall tension consequently leads to hypertrophy and stiffening of the left ventricle requiring a greater effort from the heart to maintain normal circulation. It has been estimated that approximately 50% of hypertensive patients would

die from either coronary heart disease or congestive heart failure, 33% from stroke and 10-15% from renal failure if hypertension were to go untreated (Kaplan, 1997).

The therapeutic effects of pharmacological therapy in the treatment of hypertension have been confirmed by several investigators (Curb et al., 1996; Fuchs et al., 1997; Staessen et al., 1997; Staessen et al., 1998a; 1998b; Tuomilehto et al., 1999). A number of reports have shown that calcium channel blockers, angiotensin-converting enzyme inhibitors, beta-blockers and diuretics have the ability to normalize blood pressure and to reduce the risk of cardiovascular disease and mortality in the hypertensive population (Campione et al., 1966; Helgeland, 1980; MRC, 1992; Toyoshima et al., 1997). In a recent study, Tuomilehto and associates (1999) examined the effects of calcium channel blockers in older patients with systolic hypertension (systolic blood pressure of 160-219 mm Hg and diastolic blood pressure below 95 mm Hg). Subjects were treated with nitrendipine and with the possible addition of enalapril or hydrochlorothiazide while control subjects were treated with matching placebo tablets. After a two year follow-up, the investigators reported a difference in systolic and diastolic pressures between the two groups of 10.3 and 4.5 mm Hg, respectively. In addition, overall mortality was reduced by 55% (from 45.1 deaths/1000 patients to 26.4 deaths/1000 patients), cardiovascular events decreased by 26% and fatal and nonfatal strokes decreased by 38%. Tuomilehto et al. (1999) concluded that antihypertensive therapy was beneficial in older patients with isolated systolic hypertension.

A potential limitation in treating hypertension with pharmacological agents is the risk of undesirable side effects such as faintness, nervousness, mouth dryness, insomnia,

genitourinary disturbances and palpitations (Campione, 1966, Keinanen-Kiukaanniemi et al., 1997; Toyoshima et al. 1997; Conlin & Williams, 1998; Menefee, 1998). Toyoshima and colleagues (1997) found that 49% of Japanese patients with well-controlled blood pressure (<160/95 mm Hg) reported at least one side effect while on antihypertensive therapy. Furthermore, they reported that a significantly greater number of patients with poorly-controlled blood pressure (61%) expressed a high incidence of side effects due to their hypertensive treatment. The impact of negative side effects caused by pharmacological treatment warrants further investigation into potential non-pharmacological methods to treat hypertension.

Lifestyle modifications such as dietary restriction of sodium intake, reduced alcohol consumption and regular exercise have been shown to be potential contributors to attenuating blood pressure in hypertensive patients (Fuchs et al., 1997). Regular exercise has been recommended as a useful adjunct to pharmacological therapy for its positive influence on lowering blood pressure (Cade et al., 1984; Motoyama et al., 1998). Indeed, exercise might offer individuals taking medication the option to reduce the amount and perhaps the dosage frequency needed to maintain their blood pressure.

Early reports of exercise training and cardiovascular adaptations showed that endurance exercise was optimal for attenuating blood pressure (Hagberg et al., 1983; Cade et al., 1984; Duncan et al., 1985; Kiyonaga et al., 1985), while resistance training and isometric training were contraindicated because of the high pressor response evoked during a contraction (MacDougall et al., 1985). It has now been shown that resistance training may also have potential benefits in lowering blood pressure. Presently, the

findings are equivocal, with some studies showing decreases (Frick et al., 1963; Harris et al., 1967) in blood pressure while others have shown no change (Eckblom et al., 1968; Gilders et al., 1989). Most recently, isometric training has received attention regarding its effects on lowering blood pressure (Wiley et al., 1992; Ferguson & Brown, 1997). However more research is needed to substantiate this effect.

Some investigators have proposed potential mechanisms associated with an attenuated blood pressure response following isometric training (Somers et al., 1992; Wiley et al., 1992). Since mean arterial pressure changes occur in response to changes in cardiac output or total peripheral resistance, alterations in either or both of these components might be reflective of the blood pressure changes elicited by training. Another physiological adaptation associated with the hypotensive effect of training is a change in modulation of the autonomic nervous system. Either a decrease in sympathetic activity or an increase in parasympathetic activity could result in an attenuated blood pressure response. To gain a better understanding of the associated mechanisms, investigation of one or more of these parameters is required.

Heart rate variability analysis both in the time domain and the frequency domain has been used by researchers and clinicians as a non-invasive tool for the assessment of autonomic function in healthy and diseased individuals (Kamath et al., 1993; Task Force, 1996). This method has been extensively used to assess cardiovascular responses to exercise (Kamath et al., 1991) various pharmacological agents (Alcalay et al., 1992) and to physiological maneuvers such as orthostatic stress (Weise et al., 1987). Furthermore, heart rate variability has been utilized to investigate autonomic function or dysfunction in

various disease states (Akselrod et al., 1981; Fallen et al., 1988; Panina et al., 1995). One of the potential benefits of measuring heart rate variability in the frequency domain is the ability to identify frequency specific oscillations in heart rate signals that correspond to distinct physiological mechanisms and thereby provide an estimation of neurocardiac regulation. It is possible to assess changes in autonomic modulation following a training regimen by observing the low and high frequency power components that represent the sympathetic and parasympathetic nervous systems, respectively.

1.2 Regulation of Heart Rate

1.2.1 Introduction

In a healthy individual the heart beats approximately 100,000 times over the course of a twenty-four hour period (Kamath & Fallen, 1993). Heart rate is normally determined by the inherent rhythmicity of the sinus node, otherwise referred to as the pacemaker of the heart (Malik & Camm, 1995). A heart beat is initiated by the spontaneous generation of an action potential which involves the movement of sodium and calcium ions into myocardial cells, subsequently pushing the membrane toward its depolarization threshold (Berne & Levy, 1992). The sinus node is a small, flat, ellipsoidal shaped strip of specialized cells, located in the upper lateral wall of the right atrium (Guyton, 1991). An impulse, upon arrival at the sinus node, is transmitted directly to the atrial fibres and travels to the atrioventricular node (AV node) where there is a brief delay of approximately 0.1 seconds to allow the atrial contents to be ejected into the

ventricles. Following the delay, the impulse continues to travel through the internodal pathways to the Purkinje fibres and Bundle of His (Guyton, 1991).

If the heart is not under neurohumoral influence it will beat at the intrinsic rate of the sinus node at approximately 100 to 120 beats/minute (Malik & Camm, 1995). If an impulse originates from the ventricular region of the heart it is considered an ectopic pacemaker and thus is referred to as an ectopic beat. Most often, ectopic beats are premature beats that are followed by a compensatory pause (Kamath et al., 1995).

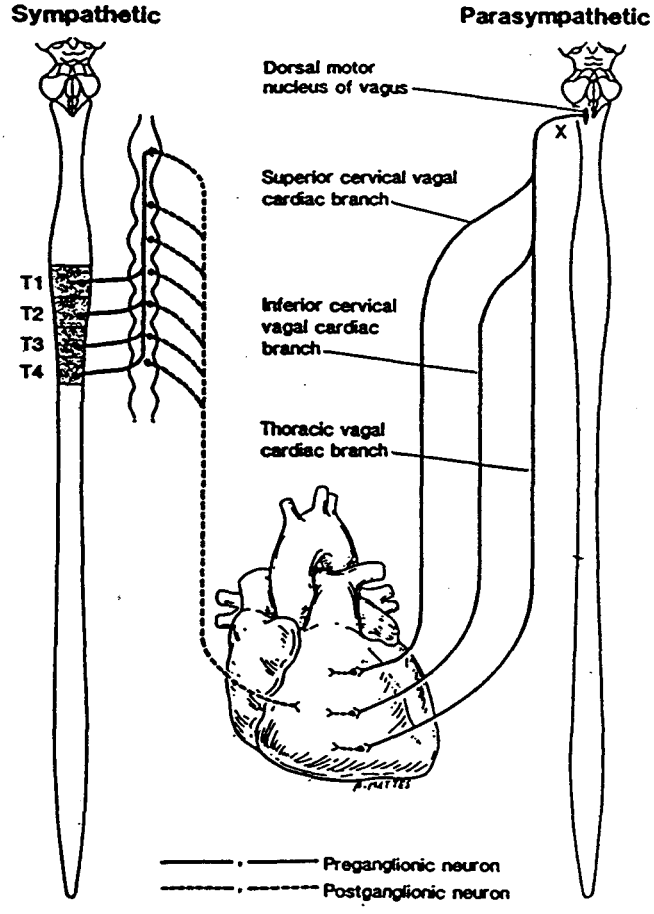

Diagram 1. Diagram depicting the nerve supply to the heart from the sympathetic and parasympathetic nervous systems (From Hockman, 1987.)

The autonomic nervous system is composed of two functional divisions, the parasympathetic nervous system and the sympathetic nervous system. Continuous beat-to-beat control of the heart rate is modulated by an interplay of the parasympathetic and the sympathetic nerve impulses delivered from control centers in the brain to the sinus node (Guyton, 1991; Kamath & Fallen, 1993). Under normal circumstances, the heart rate represents the net effect of the parasympathetic nerves and the sympathetic nerves which act in an antagonistic fashion (Levy, 1971) to decrease and increase heart rate, respectively (Diagram 1).

1.2.2 Parasympathetic Nervous System (PNS)

The parasympathetic (vagal) nerves originate in the dorsal motor nucleus and the nucleus ambiguus and lie alongside the carotid arteries in the neck, then enter the thorax (Malik & Camm, 1995). The parasympathetic system has both preganglionic and postganglionic neurons. The preganglionic neurons travel to the specific organ under control and the postganglionic neurons are located in the walls of the organ (Guyton, 1991).

In the heart, the vagus nerves mainly innervate the sinus node and AV node and to a lesser extent the atrial and ventricular muscles (Guyton, 1991). When the parasympathetic nerves to the heart are stimulated, the neurotransmitter acetylcholine is released from the terminal endings of the cholinergic nerve fibers where it is synthesized. Acetylcholine activates two types of parasympathetic receptors called muscarinic and

nicotinic receptors. Muscarinic receptors are found in effector cells and are stimulated by parasympathetic postganglionic neurons whereas nicotinic receptors are found in the synapses between the preganglionic and postganglionic neurons of the parasympathetic system (Guyton, 1991).

Acetylcholine acts to increase the permeability of myocardial cells to the outward flow of potassium ions during repolarization (Berne & Levy, 1992). In this way, the rhythm of the sinus node and the excitability of the AV junctional fibres is decreased, subsequently slowing impulse transmission to the ventricles. If parasympathetic stimulation is strong enough, it can actually stop the heart from beating for short periods of time (Malik & Camm, 1995).

1.2.3 Sympathetic Nervous System (SNS)

The nerves of the sympathetic nervous system originate in the intermediolateral column of the spinal cord in the upper thoracic and upper lumbar region (Guyton, 1991; Malik & Camm, 1995). The sympathetic system has two types of neurons, preganglionic and postganglionic. The cell bodies of preganglionic neurons lie in the intermediolateral horn of the spinal cord and the postganglionic neurons originate in the sympathetic chain ganglia (Guyton, 1991).

Sympathetic nerves are distributed to all portions of the heart including the atrial and ventricular muscles. When the sympathetic system is stimulated, adrenergic neurotransmitters epinephrine and norepinephrine are released from two locations, the sympathetic terminal nerve endings and the adrenal medulla. Both have the same

stimulatory effects except the duration in the alteration of cardiovascular function is more prolonged with the humoral release from the adrenal medulla (Astrand, 1986; Berne & Levy, 1992; Guyton & Hall, 1996).

Norepinephrine acts by increasing membrane permeability of myocardial cells to the slow inward currrents of sodium and calcium ions that are responsible for the spontaneous generation of an action potential. This leads to a more rapid depolarization resulting in an increase in heart rate (Guyton & Hall, 1996). In addition, norepinephrine increases conduction of depolarization through the heart to augment contractility of the myocardium.

1.2.4 Cardiac Reflexes

The autonomic nervous system has a central command center that controls overall autonomic activity. However, there are several reflexes that react as a feedback control system in response to the demands of the autonomic nervous system. For example, the most well-known mechanism to control changes in arterial pressure is the baroreceptor reflex (Malik & Camm, 1995). Baroreceptors or stretch receptors are located in the walls of the systemic arteries, primarily in the carotid sinus and the aortic arch. When there is an increase in blood pressure, the baroreceptors respond to the arterial distention by transmitting a feedback signal to the cardiovascular control centre in the medulla which results in autonomic lowering of heart rate and in turn restores blood pressure to its lower level (Guyton, 1991). In this way, the baroreceptors function to maintain arterial blood pressure within a normal physiological range.

1.3 Heart Rate Variability

1.3.1 Historical Perspectives

Hemodynamic parameters such as instantaneous heart rate and arterial blood pressure are known to fluctuate on a beat-to-beat basis. The earliest documentation of beat-to-beat variability was by Stephen Hales (1733) who observed a correlation between respiratory cycle, blood pressure level and inter-beat interval (R-R interval) during a quantitative measurement of arterial blood pressure. Over two centuries later, Hon et al. (1965) demonstrated the clinical importance of beat-to-beat variation in fetal monitoring and postulated that variations in fetal heart rate were modulated on a beat-to-beat basis by the parasympathetic and sympathetic nervous systems.

The beat-to-beat variability in hemodynamic parameters was believed to reflect changes in cardiovascular control centers occurring in response to exogenous (i.e. environmental stress) and endogenous (i.e. variations in intrathoracic pressure) perturbations (Appel et al., 1989). Short-term cardiovascular control was believed to primarily involve the PNS and SNS and to some degree the renin-angiotensin system (Gutmann et al., 1973), although no direct evidence for the latter is currently available.

Measurement of heart rate variability in the frequency and time domains has been shown to be an important non-invasive investigational method and clinical tool to assess autonomic nervous system function (Fallen et al., 1988; Kleiger et al., 1992; Ori et al., 1992; Kamath et al., 1993). Heart rate variability has been used to assess autonomic responses to exercise (Kamath et al., 1991; Yamamoto et al., 1991), various physiological

maneuvers (Weise et al., 1987; Lipsitz et al., 1990; Jasson et al., 1997; Malliani et al., 1997), mental stress (Lucini et al., 1997a), and pharmacological agents (Alcalay et al., 1992; Cowan et al., 1993; Hohnloser et al., 1993). In addition, heart rate variability has been used as a significant predictor of mortality following a myocardial infarction (Kleiger et al., 1987; Bigger et al., 1992), in congestive heart failure (Saul et al., 1988; Casolo et al., 1991; Panina et al., 1995), following cardiac transplantation (Fallen et al., 1988), in hypertension (Bristow et al., 1969; Guzetti et al., 1988; Lucini et al., 1997b) and in chronic renal failure (Axelrod et al., 1987). Furthermore, measures of heart rate variability have allowed assessment of changes in autonomic function with aging (Hellman et al., 1976; Waddington et al., 1979; Collins et al., 1980; Finley et al. 1987, 1995; Lipsitz et al., 1990; Schwartz et al., 1991; Ziegler et al., 1992; Ryan et al., 1994; Tsuji et al., 1994; Craft et al., 1995; Liao et al., 1995; Harvey, 1996).

Spectral components of heart rate variability have been explored from short-term (Sayers, 1973; Akselrod et al., 1981; Hirsch & Bishop, 1981; Pagani et al., 1986) and long-term electrocardiographic recordings (Saul et al., 1988; Malik et al., 1993; Pinna et al., 1994) using frequency and time domain indices. Specific measurements for characterizing heart rate variability in the time and frequency domain exist independently, in order to assess modulation of the autonomic nervous system.

1.3.2 Frequency Domain Analysis of Heart Rate Variability

Sympathovagal variations in heart rate can be evaluated using a number of methods. One of the more commonly used methods to assess neurocardiac modulation is

through a frequency domain analysis (power spectrum) of the heart rate variability signal. Frequency domain analysis of heart rate variability involves the decomposition of the heart signal or R-R interval tachogram into sine waves or distinct frequency components where each component is quantified in terms of its relative intensity, also termed power (Cohen, 1989). Power spectral analysis of the raw electrocardiogram (ECG) signal can be performed using one of two methods, autoregressive analysis or fast fourier transformation (FFT). Autoregressive analysis provides a continuous smooth spectrum of activity and FFT is characterized by discrete peaks for each frequency component (Ori et al., 1992). With these methods, the power spectrum displays the squared amplitude of the sine waves as a function of frequency obtained over a recording period of 128 seconds (Kamath & Fallen, 1993).

Requirements and recommendations have been established to ensure that frequency domain recordings produce reliable and reproducible spectral estimations (Task Force, 1996). The following parameters are included in the criteria: the signal must be stationary so the power spectral density of the heart rate variability signal is robust; the sampling period must be long enough to obtain power spectral data; and the signal must be sampled at an adequate rate (Ori et al., 1992; Kamath & Fallen, 1993; Cerutti et al., 1995; Task Force, 1996). In addition, ectopic beats are eliminated from the recording by using appropriate interpolation techniques to avoid contamination of the power spectrum (Ori et al., 1992, Parati et al., 1995a; Task Force, 1996).

In an important study, Akselrod et al.(1981) measured the power spectrum of heart rate fluctuations in conscious unanesthetized dogs by selectively blocking

cardiovascular control systems with specific pharmacological agents. They found that short-term fluctuations in cardiovascular parameters were concentrated in three principal spectral peaks ranging from 0 to 0.5 Hz as was previously described by Sayers et al.(1973) in humans. Included was a high frequency (HF) peak believed to correspond to parasympathetically mediated respiratory sinus arrhythmia observed between 0.20 to 0.35 Hz; a low frequency peak (LF) evident between 0.12 to 0.04 Hz believed to be under both parasympathetic and sympathetic control and a mid-frequency peak at approximately 0.12 Hz corresponding to baroreceptor modulation of heart rate (Akselrod et al., 1981; Pagani et al., 1986; Task Force, 1996). Two other peaks in the lower frequencies have also been identified following 24-hour ECG recordings (Saul et al., 1988; Stein et al., 1994). A very low frequency (VLF) peak which is not always present has been shown to exist at frequencies between 0.01 and 0.04 Hz and has been attributed to thermoregulation, peripheral vasomotor activity and activity of the renin-angiotensin system (Ori et al., 1992; Kamath & Fallen, 1993). This band is normally filtered out to avoid contaminating the signal due to a low signal to noise ratio (Ori et al., 1992; Kamath & Fallen, 1993; Cerutti et al., 1995; Task Force, 1996). The heart may fluctuate with even longer periodicities ranging from 10^{-2} to 10^{-5} Hz and fluctuations in this range have been designated as the ultra low frequency peak (ULF) (Stein et al., 1994).

Pharmacological intervention studies have shown that with the administration of muscarinic blocking agents glycopyrrolate and atropine, the HF peak in the power spectral plot was abolished (Akselrod et al., 1981; 1985; Pomeranz, 1985; Rimoldi, 1990). Similarly, with administration of propranalol, a beta-sympathetic blocking agent

and phentolamine an alpha-sympathetic blocking agent, the LF peak in the power spectral plot was diminished (Akselrod et al., 1981). The LF peak was not completely abolished with sympathetic blockade, which indicated that the low frequency fluctuations in heart rate must be jointly mediated by the SNS and PNS (Akselrod et al., 1985). Furthermore, by administering angiotensin converting-enzyme inhibitor, blockade of the renin-angiotensin system was achieved. Thus, pharmacological blockade of specific cardiovascular control systems has proven to be a useful means of identifying parasympathetic and sympathetic modulation of the autonomic nervous system.

LF and HF components of power spectral analysis are evaluated in terms of frequency (hertz) and amplitude (Malliani et al., 1991). The power of the spectral peaks is assessed by the area, thus, total power of a signal can be determined by viewing the total area under the power spectral curve (Ori et al., 1992). In the same vein, power of an individual frequency component is represented by the area under the portion of the curve related to the component (Ori et al., 1992). Therefore, squared units (milliseconds) are used to express the absolute value. Usually, values are presented as normalized units which can be obtained by dividing the power of a given component by the total variance (from which component one has been subtracted) and multiplying by 100 (Malliani et al., 1991).

1.3.3 Time Domain Analysis of Heart Rate Variability

A commonly used method in clinical studies in cardiology to assess heart rate variability is time domain analysis. Time domain analysis can provide information about

heart rate length based on short term (i.e. 5 to 30 min.) and long term (i.e. 24 hour) ECG recordings. This method is useful in assessing heart rate variability in survivors of acute myocardial infarction (Kautzner et al., 1995), congestive heart failure (Van Hoogenhuyze et al., 1991), and in response to pharmacological intervention (Cook et al., 1991), physiological maneuvers (Jasson et al, 1997), and psychological stress (Kleiger et al., 1995).

Short term time domain measures such as mean heart rate and standard deviation of heart rate can be obtained over controlled recording periods of 5 to 30 minutes (Chipps et al., 1981; Ewing et al., 1985). The measurement of heart rate over a short period of time has been shown to provide an index of vagal activity (Kleiger, 1992). Time efficiency is one of the benefits of using short term measurements to assess heart rate variability since it requires only several minutes to obtain a recording. However, limitations include the need for other measurements, in addition to requiring patient cooperation which in some cases might not always be possible (terminally ill or weak patients) (Kleiger et al., 1992).

Long term time domain measures can be obtained using 24-hour ambulatory Holter ECG monitoring. Mean and standard deviation of the R-R interval signal can be calculated over the entire recording period. From the continuous ECG recording, QRS complexes are detected, identified and any non-sinus beats (including artifact and ectopic beats) are recognized and eliminated from the analysis (Kamath & Fallen, 1993). An R-R interval series is formed from their measurements. Time domain parameters are commonly identified in two separate classes, 1) measures based on beat-to-beat intervals

(N-N intervals); and 2) measures based on the difference between adjacent cycles (Kleiger et al., 1992; Task Force, 1996). Variables that are derived from the beat-to-beat intervals reflect broadly based measures of HRV where they are influenced by both short term (i.e. respiration) and long term (i.e. circadian and secular trends) factors. The variables that are derived from the difference between adjacent cycles reflect short term HRV measured over a longer period of time and are thought to be mediated by the PNS (Kleiger et al., 1992; 1995; Stein et al., 1994).

Time domain measures based on beat-to-beat intervals are variables that are derived from the R-R interval series. These include mean heart rate and standard deviation of the normal to normal R-R intervals (SDNN) over the entire recording period. Another time domain variable derived from beat-to-beat intervals includes standard deviations of the 5-minute mean cycle lengths over the entire recording period (SDANN). This provides an index of the average 5-minute interval variability over 24-hours (including diurnal variations) but does not allow assessment of short term variability. In addition, the mean of the standard deviation of 5-minute cycle intervals over the entire recording period (SDNNIDX) estimates the variability related to cycle lengths that are less than 5-minutes in length (Kleiger et al., 1995).

The second class of time domain measures based on the difference between adjacent cycle lengths includes the root mean squares of successive differences (rMSSD). In addition, variables that reflect the proportion of differences include the proportion of cycles where the difference is >50 milliseconds (pNN50) and the proportion of cycles

where the difference is >6.25% of the mean heart period (pNN6.25%) (Kleiger et al., 1995).

In a study by Kautzner et al.(1995), the two day reproducibility of time domain heart rate variability indexes and the relation between individual time domain measures were examined in a population of acute myocardial infarction survivors. Analysis of the time domain indices revealed that reproducibility of the pNN50 index was significantly inferior to the rest of the measures from Day 1 to Day 2 with a mean value of relative error being 45 ± 45%. Aside from this finding however, all other time domain variables were stable and reproducible. In the same study, correlations between individual time domain variables were relatively high especially between SDNN and SDANN (Day 1 correlation = 0.93 and Day 2 correlation = 0.92). In addition, pNN50 and rMSSD, variables describing the short term index of heart rate variability similarly showed a high correlation (Day 1 correlation = 0.87 and Day 2 = 0.99) (Kautzner et al., 1995). The high correlation among short term time domain variables found by Kautzner et al. (1995) has been supported by other investigations in normals and in patients with low (< 50ms) and high (> 50ms) cycle length variability (CLV) (Bigger et al., 1992; Kleiger et al., 1995).

Although there is a high level of reproducibility among time domain measures which has advantages for recording circadian variations and for the assessment of clinical interventions, there has been some uncertainty as to the methodology of these measures (Kleiger et al., 1992; 1995; Kamath & Fallen, 1993). The uncertainty stems from the inability to control the patient's dynamic state during the recording period, thereby creating a bias on the time domain statistics making it difficult to interpret. For this

reason, patients are often asked to keep activity journals during the recording period to assist in the clinical interpretation of the recording (Harvey, 1996).

1.3.4 Influence of Respiratory Sinus Arrhythmia on Heart Rate Variability

The term respiratory sinus arrhythmia (RSA) reflects the phasic relationship between shortening and lengthening of the heart period with inspiration and expiration, respectively (Berne & Levy, 1992). Evidence of the effects of rhythmic variations on heart rate has been well documented (Katona et al., 1975; Hirsch et al., 1981; Eckberg et al., 1983; Seals et al., 1990; Brown et al., 1993; Novak et al., 1993). Respiratory effects on heart rate are mediated in part, by reflex and central factors (Levy, 1966; Berne & Levy, 1992, Novak et al., 1993). During inspiration there is a decrease in intrathoracic pressure that results in an increase in venous return to the right atrium. The increase in pressure on the right side of the heart stimulates atrial receptors located in the venoatrial junctions to increase heart rate (Berne & Levy, 1992). A subsequent increase in stroke volume on the left side of the heart increases arterial pressure which invokes the baroreceptor reflex. Upon expiration, intrathoracic pressure returns to baseline and the atria are unloaded. Subsequently, heart rate and arterial pressure return to pre-inspiration levels (Novak et al., 1993).

Early experiments conducted to assess RSA and the relative roles of the PNS and the SNS revealed that contribution to RSA was produced by both divisions of the autonomic nervous system, although the influence of the PNS predominated (Levy,

1966). Despite bilateral vagotomy, RSA was still present, although the amplitude of the fluctuations was reduced.

Several investigations have examined the influence of the autonomic nervous system on RSA and have found that during inspiration, vagal activity was diminished and sympathetic activity was accentuated (Hirsch & Bishop, 1981; Eckberg, 1983; Brown et al., 1993; Novak et al., 1993). However, during expiration, the opposite effect was seen, that is, vagal activity was accelerated and sympathetic activity was inhibited. Thus, it has been demonstrated that RSA might be a valid non-invasive means of quantifying parasympathetic control of the heart (Levy et al., 1966; Katona & Jih, 1975; Kollai & Mizsei, 1990).

Katona & Jih (1975) examined the effects of cardiac vagal efferent activity during RSA in seven anesthetized dogs under several conditions by repeatedly and reversibly blocking the vagi. They reported that when the vagi were bilaterally cooled, the average heart period and RSA was decreased. Upon warming however, average heart period and RSA were restored to their precooling values. In addition, they observed that cessation of vagal efferent activity during the inspiratory phase occurred even in the presence of elevated levels of blood pressure. The results of Katona & Jih (1975) suggested that in anesthetized dogs, changes in the amplitude of RSA fluctuations indicated proportional changes in cardiac vagal tone.

Kollai & Mizsei (1990) explored the applicability of the methods used by Katona & Jih (1975) in human subjects. They examined changes in heart period and RSA in response to intravenous propranolol (a sympathetic nervous system blocking agent). In

patients treated with propranolol, average heart period was significantly increased from 870 ± 16ms to 1092 ± 19ms. In addition, RSA was also significantly increased from 108 ± 12ms to 142 ± 15ms. Kollai & Mezsei (1990) concluded that human respiratory modulation of cardiac parasympathetic activity was not completely abolished during inspiration since the minimum heart period in humans was further reduced by physiological interventions (handgrip, orthostatic tests). These results differ from those of Katona & Jih (1975) who found that in anesthetized dogs, the inspiratory level of vagal activity was completely eliminated. Thus, a direct inference cannot be made to humans from experiments performed on anesthetized animals. Furthermore, it was confirmed that although a significant correlation existed between RSA and parasympathetic control, the relationship was not close ($r = 0.61$), hence, variations in the magnitude of RSA may not necessarily reflect proportionate changes in cardiac vagal control.

Investigation of the effects of RSA on heart rate modulation has been centered around its appearance in the presence of rhythmic breathing movements. Some studies have presented evidence that RSA occurs at the onset of an inspiratory breath hold (Clynes, 1960; Davies & Neilson, 1967; Valentinuzzi & Geddes, 1974; Hirsch & Bishop, 1981) indicating that respiratory movements are not necessary for RSA appearance. Indeed, further investigation into the effects of breathing frequency, tidal volume and static lung volume on RSA amplitude has been performed (Hirsch & Bishop, 1981; Eckberg, 1983; Brown et al., 1993).

Brown et al. (1993) explored the relationship between controlled breathing frequencies and tidal volumes and their association to R-R interval power spectra.

Breathing frequency was controlled at seven different respiratory rates (ranging from 6 to 24 breaths/minute) at tidal volumes of 1,000 and 1500ml. They observed a decrease in R-R variability as the breathing frequency increased. In addition, it was noted that at breathing frequencies of greater than 10 breaths/minute, levels of R-R interval power spectra were reduced. The results indicated that changes in respiratory rate largely influenced both LF (0.06 – 0.14 Hz) and respiratory frequency (0.17 – 0.33 Hz) R-R power spectra. Furthermore, at a larger tidal volume (1500 ml), the R-R interval power spectra was higher, although breathing frequency did not alter average R-R interval significantly. In their review of existing literature, Brown et al. (1993) reported that only about one half of the studies controlled for respiratory rate and about one third involved measurement of tidal volumes. The results of their study highlight the importance of measuring respiration and tidal volume to accurately interpret R-R interval power spectra.

The aforementioned investigations have signified the rationale behind measurement of respiratory rate and tidal volumes if HRV spectral analysis is to be used as a viable tool in clinical assessments. As described by Eckberg (1983) and Brown et al. (1990), breathing frequency appears to have a greater influence on RSA than tidal volume, therefore, the future direction of investigations should incorporate measurement of these parameters at least, as a minimum standard for HRV power spectral analysis.

1.3.5 Use of Physiological Maneuvers in Heart Rate Variability

The heart rate and blood pressure responses to various physiological conditions including orthostatic stress (Montano et al., 1994), passive tilt (Pagani et al., 1986; Task

Force, 1996; Jasson et al., 1997; Malliani et al., 1997), the Valsalva maneuver (Shimada et al., 1986a) and postural changes (Lipsitz et al., 1990; Lucini et al., 1997a) have been well documented. Evaluation of the power spectral analysis of HRV during various experimental conditions has provided useful information about autonomic control of the heart. Specifically, investigators are better able to distinguish between and even quantify the separate contributions to HRV made by the parasympathetic and sympathetic nervous systems. Not only is HRV a viable tool in clinical assessments of physiopathological conditions such as hypertension (Malliani et al., 1991) and ischemic heart disease (Lombardi et al., 1987), but it is also a very simple procedure with reproducible spectral responses.

Pagani et al. (1986) examined the relative roles of the two divisions of the autonomic nervous system in conscious dogs and healthy humans at rest and in response to orthostatic stress. They demonstrated that passive tilt to an upright 90° position resulted in a large increase in the LF component of heart rate power spectra from 58 ± 3% at rest to 90 ± 1% during tilt. In addition, the LF to HF ratio had increased from 3.6 ± 0.7% to 21 ± 4%. The marked increase in the LF component and decrease in the HF component of the autospectrum in response to the postural change indicated an enhanced sympathetic drive to the heart.

The characteristic heart rate response to physiological perturbations such as postural changes (from supine to standing) or passive tilt involves a significantly enhanced sympathetic response indicated by the increased LF power on the autospectra. A simultaneous reduction in vagal input to the heart also occurs as indicated by a

decrease in the HF power band (Pomeranz et al., 1985; Malliani et al., 1991; Kamath & Fallen, 1993). Investigators of HRV have clearly acknowledged the fact that an interaction between sympathetic and parasympathetic efferent activity on the heart could be assessed by examining the impact of physical stress on HRV.

1.3.6 Effects of Aging on Heart Rate Variability

A diminution in the integrity of the autonomic nervous system has been shown to occur with advancing age (Johnson & Spalding, 1974). It is thought that differences in HRV between age groups are mainly due to a decline in PNS function (Pfeffer et al., 1983). Several investigations have explored the relationship between aging and HRV (Waddington et al., 1979) and have reported a reduction in HRV and a reduced heart rate response to standing (O'Brien et al., 1986; Simpson & Wicks, 1988), postural tilt (Lipsitz et al., 1990), the valsalva maneuver (O'Brien et al., 1986; Appenzeller, 1990) and to a single deep breath (O'Brien et al., 1986). In addition, the magnitude of RSA has been shown to differ across age groups (Schlomka, 1937; Hellman & Stacey, 1976). Increased peripheral vascular resistance and a loss of arterial wall elasticity with aging have also been documented (Swales, 1979; Simpson & Wicks, 1988).

To assess the effects of aging on HRV, O'Brien et al. (1986) studied 310 subjects ranging in age from 18 to 85 years. The groups were separated by decade (20 to 70 years) and there was a minimum of 50 subjects in each group. Heart rate data were collected on all subjects in the supine position, during a single deep breath, during the Valsalva maneuver and upon standing. A non-linear decline in heart rate responsiveness

with increasing age was observed which appeared to be steeper in the younger than in the older subjects. In addition, multiple regression analysis showed that age accounted for 15 to 33% of the variation in heart rate.

Pagani and associates (1986) investigated the relative roles of the parasympathetic and sympathetic systems to determine HRV at rest and in response to 90° postural tilt in subjects ranging in age from 20 to 60 years old. Subjects were divided into three groups identified as young (20 to 30 years), mid (30 to 45 years) and old (45 to 60 years). Their results confirmed that HRV had a significant age dependency. They reported that the duration of R-R intervals decreased with increasing age, both at rest and during upright tilt ($r = 0.70$ at rest, and $r = 0.60$ during tilt). In addition, mean R-R interval increased with age, while R-R variance was significantly lower. During tilt, the older subjects demonstrated a significantly longer R-R interval with less variance compared to the younger subjects. However, when the autospectra for the three groups were compared, the older group showed only a minor reduction in the power of the LF component and a slightly greater power in the HF component. Interestingly, there was no comparative difference in the LF to HF ratio in the three groups at rest or during tilt. The investigators suggested that aging was characterized by a new equilibrium between the two divisions of the autonomic nervous system. The results reported by Pagani et al. (1986) have recently been confirmed by other investigators (Craft & Schwartz, 1995; Liao et al., 1995).

Investigation into factors such as physical conditioning, which may influence the rate of decline in HRV with age has been initiated, but further research in the area is

warranted. Presently, there is some evidence to suggest that regular exercise may modify the decline in HRV with age (Hellman & Stacey, 1976; Hirsch & Bishop, 1981). Hellman & Stacey (1976) attempted to correlate physical condition parameters with the amount of RSA experienced in young (21 to 39 years) and old (40 to 65 years) subjects. It was interesting to note that 4 of 5 subjects that were in poor physical condition exhibited negative deviations (mean of –33%) from the predicted value. In addition, 3 of 4 subjects who were overweight at the time of the investigation also showed negative deviations with a mean of –29% of the predicted value. Similar negative deviations were obtained for subjects that were predisposed to personal and/or familial history of heart disease. Two subjects that were in good physical condition demonstrated a positive deviation from the predicted value, indicating that perhaps there was a correlation between RSA and physical condition.

In an investigation by Hirsch & Bishop (1981), it was reported that in healthy physically active subjects over the age of 35 years, RSA was maintained. In fact, in two subjects that regularly engaged in exercise (a 37-year-old subject and a 78-year-old subject), the RSA values for each subject were similar. It is possible that the selection of subjects in Hirsch & Bishop's (1981) study may have been biased toward active healthy subjects. However, if maintenance of a healthy lifestyle into old age can prevent or even reverse the age-associated decline in HRV, there could be positive benefits to advocating exercise in elderly populations.

1.4 Effects of Hypertension on Heart Rate Variability

1.4.1 Introduction

The physiological adaptations that occur in response to a sustained increase in arterial pressure include an enlarged ventricular wall caused by a greater effort required to maintain normal circulation. As well, a thickened inelastic arterial wall becomes resistant to blood flow which is manifested by increased total peripheral resistance (Morhman, 1997; Kaplan, 1997). In addition, resetting of arterial baroreceptors (Bristow et al., 1969; Mancia et al., 1983; Robbe et al., 1987; Parati, 1995b), increased plasma catecholamine levels (Julius & Esler, 1975; Guzzetti et al., 1988) and alterations in neural regulatory activity have also been observed (Alicandri et al., 1985; Pagani et al., 1986; Guzzeti et al., 1988) during and following exericse.

1.4.2 Baroreceptor Reflex Sensitivity in Hypertension

Arterial baroreceptors, located in the walls of the aortic arch and carotid sinus work toward maintaining and regulating arterial blood pressure within normal physiological limits. However, in hypertension, where blood pressure is maintained at a higher than normal level, the baroreceptor response is significantly altered and they become "reset" to meet the changing demands of the cardiovascular system (Kamath & Fallen, 1993; Parati, 1995b). Several investigators have reported an impairment or reduced sensitivity of arterial baroreceptor responsiveness in hypertensive patients (Bristow et al., 1969; Mancia et al., 1983; Robbe et al., 1987). Baroreceptor reflex sensitivity can be assessed by phenylephrine injection, a drug that increases arterial blood

pressure. With each incremental increase in blood pressure, a parallel decrement in heart rate occurs. The interbeat interval slope versus the rise in systolic blood pressure in response to the injection signifies the baroreceptor reflex sensitivity in milliseconds per millimeter of mercury (Sleight, 1979; Vann Jones & Bannister, 1988).

Bristow et al. (1969) examined the effects of angiotensin and phenylephrine administration on baroreflex response in 30 normotensive and hypertensive subjects. Injection of these drugs led to increased arterial pressures. The results showed that the average slope of the systolic blood pressure R-R interval distributions for the hypertensive subjects was significantly lower than that for the normotensive subjects (2.8 $\pm$ 0.6 msec/mm Hg vs 12.8 $\pm$ 2.0 msec/mm Hg, respectively). It was hypothesized that the large difference in slope between the groups demonstrated a decreased baroreceptor reflex sensitivity in essential hypertension, with respect to heart rate. This diminished baroreceptor response could have resulted from a reduced compliance of arterial walls in the aortic arch or carotid sinus, allowing little stretch per unit rise in blood pressure (Bristow et al., 1969).

To corroborate the findings of Bristow et al. (1969), Mancia and colleagues (1983) studied the arterial baroreceptor control of heart rate in 38 normotensive, mild, and severely hypertensive subjects (mean blood pressure less than 100 mm Hg, between 101-115 mm Hg and above 115 mm Hg, respectively). Baroreceptor sensitivity was assessed using either phenylephrine or trinitroglycerine injection. The results indicated a marked reduction in arterial baroreceptor control in the severely hypertensive subjects compared with the normotensive and mildly hypertensive subjects.

1.4.3 Plasma Catecholamine Levels in Hypertension

Individuals with borderline hypertension (Julius & Esler, 1975) and in some cases with essential hypertension (Frohlich et al., 1971), have been reported to have higher heart rates compared with normotensives. A potential mechanism associated with increased heart rate includes an enhanced sympathetic tone. However, studies employing plasma levels of circulating catecholamines as an index of sympathetic tone are controversial (Julius & Esler, 1975; Agabiti-Rosei et al., 1982; Goldstein, 1983; Guzetti et al., 1988).

Plasma catecholamines, namely epinephrine has its origin in the secretions of the adrenal medulla. However, the sympathetic nerves, predominately of the heart are deemed to be the major source of plasma epinephrine (DeQuattro, 1968). There is evidence to suggest that plasma catecholamine levels are a quantitatively valid and indirect index of sympathetic nervous activity (Yamaguchi et al., 1975). Studies on patients with essential hypertension have supported the existence of elevated norepinephrine levels in plasma (Engelman; 1970; DeQuattro & Chan, 1972; Esler, 1973; Louis et al., 1973). However, in borderline hypertensive patients, the situation is controversial with findings indicating elevated plasma levels (DeQuattro & Chan, 1972), or normal levels (Louis et al., 1973).

1.4.4 Heart Rate Variability in Hypertension

The use of HRV power spectral analysis in hypertension has proved to be a useful, non-invasive technique to measure neural regulatory mechanisms (Clement et al., 1979; Alicandri et al., 1985; Pomeranz et al., 1985; Pagani et al., 1986; Guzzetti et al., 1988). By applying this technique, assessment of autonomic nervous control of the heart can be made. Previously, the LF and HF components of the power spectra have been identified and described (refer to HRV section). Briefly, the LF fluctuations in heart rate (around 0.1 Hz) have been suggested to represent joint mediation by the SNS and PNS, whereas the HF fluctuation, also referred to as the respiratory frequency band, exclusively represents PNS modulation of heart rate.

From the power spectrum of HRV in a normal healthy individual during supine rest, a small LF peak and a prominent HF peak are present which represent vagal and sympathetic modulation, respectively (Kamath & Fallen, 1993). Upon standing, the power spectrum shifts to a prominent LF peak (sympathetic modulation) and a small HF peak (parasympathetic modulation). The changes that occur from supine to standing reflect reflexive mechanisms that are activated to prevent a decrease in blood pressure (Kamath & Fallen, 1993).

Compared with normotensives, hypertensive subjects consistently demonstrate an elevated LF power and a correspondingly reduced HF power during supine and standing conditions (Alicandri et al., 1985; Pomeranz et al., 1985; Furlan et al., 1987; Guzzetti et al., 1988) indicating an elevation in sympathetic neural activity. Evaluation of acute and chronic beta-adrenergic receptor blockade has demonstrated that heart rate and blood

pressure are decreased along with a diminished LF component and an increased HF component (Alicandri et al., 1985; Guzzetti et al., 1988). Guzzetti et al. (1988) and Alicandri et al. (1985) investigated the HRV in hypertensive patients and normal controls using power spectral analysis. Both groups found that R-R interval variance in the hypertensive subjects was significantly smaller than that observed in the controls.

Power spectral analysis of HRV seems to be a potentially effective method for examining autonomic neural activity in hypertension. The ability to assess various components of the power spectrum and identify sympathetic and vagal contributions to the HRV signal is a valuable tool during clinical assessment. Pharmacological intervention studies or exercise training studies may benefit from the use of this method since it provides an accurate window into neurocardiac modulation of the beat-to-beat fluctuations in HRV and blood pressure variability.

1.5 Blood Pressure Variability

1.6 Twenty-four Hour Variability

1.6.1 Diurnal Variability

Short-term and long-term variability in blood pressure are known to occur in response to endogenous and exogenous stimuli (Baumgart, 1991; Pickering & James, 1993; Coca, 1994). For example, short-term blood pressure variability occurs on a beat-to-beat basis with the respiratory cycle where blood pressure decreases slightly with inspiration (Conway, 1986). In addition, short-term variability also reflects changes in heart rate and peripheral resistance induced by alterations in sympathetic and

parasympathetic nervous system activity (Akselrod et al., 1981). The mechanisms that affect short-term variability and the relationship between blood pressure fluctuations and heart rate variability can be assessed on a beat-to-beat basis using power spectral analysis (de Boer et al., 1985a; 1985b).

Day time variability in blood pressure has been demonstrated under many conditions including mental arousal (Conway et al., 1983), physical stress (Kerkhof et al., 1998), lifestyle stress (Pickering, 1997) and exercise (Watson et al., 1980), where the degree of variability is affected by the severity of the stimuli. Conway (1983) measured blood pressure in 13 subjects during three states of mental arousal which included a drowsy state after being awakened from sleep, a reading period where subjects were given a newspaper to read and a mental arithmetic period. Compared with average baseline values (151.5 $\pm$ 6.1 mm Hg systolic and 94.9 $\pm$ 4.2 mm Hg diastolic), blood pressure rose considerably during all three states of arousal with the highest value reaching 14.8 mm Hg ($p < 0.001$) above the resting state during mental arithmetic. The fluctuations in blood pressure that were observed during the three tasks exemplified how chronic stress or other daily activities could rapidly alter blood pressure throughout the day.

Most of the available literature on 24 hour variations in blood pressure point to a predominant role of exogenous influences on circadian variation (Mann et al., 1979; Clark et al., 1987; Baumgart, 1991). Few investigators have attempted to eliminate the possible masking influences of exogenous factors to determine if there is in fact an endogenous component to circadian variation (Minors & Waterhouse, 1984; Czeisler,

1985). Recently, Kerkhof et al. (1998) tried to minimize the effects of exogenous influences by controlling environmental and behavioural stimuli in 25 normotensive young adults. Subjects remained awake in the supine position for the duration of 26 hours. Meal consumption, liquid intake, washroom utilization and activities over the study period were controlled. This study confirmed the results of a previous investigation (Pickering et al., 1967) which showed that there was no evidence of a circadian variation in blood pressure independent of sleep and in the absence of exogenous influences suggesting that perhaps the circadian variation may be attributed to the sleep-wake cycle.

Much of the existing literature has suggested that there is a circadian variation in arterial blood pressure where nocturnal pressures tend to be lower than day time pressures (Richardson et al., 1964; Littler, 1979; Dimsdale & Heeren, 1998). Only in cases where individuals worked night-shifts or were deprived of sleep was there an absence of a nocturnal fall in pressure (Brooks & Carroll, 1912; Diehl, 1929).

1.6.2 Nocturnal Variability

During the last few decades investigators have examined blood pressure variability over a 24 hour duration and have consistently demonstrated a nocturnal fall in blood pressure during sleep, with the lowest pressure occurring during the early hours of sleep (Brooks & Carroll, 1912; Diehl, 1929; Shaw et al., 1963; Richardson et al., 1964; Littler et al., 1975; Littler et al., 1978; Drayer et al., 1982; Dimsdale & Heeren, 1998). One of the earliest investigations to document nocturnal variations in blood pressure was by Brooks & Carroll (1912) who used a simple cuff technique (pressures averaged over at

least four trials) to monitor systolic blood pressure. In thirty subjects with low pressure (average SBP 100 mm Hg), sixty-eight subjects with moderate pressure (average SBP 142.5 mm Hg) and twenty-nine subjects with high pressure (average SBP 204.5 mm Hg) a nocturnal fall was noted with a maximum drop two hours after subjects fell asleep. In addition, they found that the group of subjects with the highest day time blood pressure values showed the greatest drop in night time blood pressure measurements, which is in agreement with previous workers (Veerman et al., 1994). They also found that blood pressure remained low in the early hours of the morning but continued to rise to maximum values by late afternoon. To corroborate the results of Brooks and Carroll (1912), Diehl (1928) compared morning and evening pressures in one hundred male university students and reported that mean morning pressures (114 mm Hg) were lower than mean evening pressures (124 mm Hg). However, blood pressure variability did not differ between morning and evening pressures and there was no correlation between the height of blood pressure and blood pressure variability which contradicted the findings of other investigators (Littler et al., 1978).

Utilizing a more accurate technique to measure variability in blood pressure, Littler et al. (1975) measured direct arterial pressure continuously over 24 hours in the homes of 18 normotensives, untreated hypertensives and treated hypertensives. Interestingly they found an almost equal relative reduction in systolic and diastolic values (~ 20%) irrespective of the level of waking pressure and irrespective of anti-hypertensive treatment. However, the absolute drop was dependent on the waking pressure. To compare the aforementioned nocturnal fall in pressure, Schillaci et al. (1996) studied

diurnal blood pressure changes in 2042 untreated subjects with essential hypertension. Ambulatory monitoring was used to record blood pressure every 15 minutes throughout a 24 period and subjects were defined as 'non-dippers' if nocturnal reductions were ≤ 10% or as 'dippers' if reductions were > 10%. The results indicated that 78.3% of the subjects were identified as 'dippers', with the remaining subjects being labeled as 'non-dippers'. They noted that age played a significant role in determining whether subjects were 'dippers' or 'non-dippers' since older subjects tended to be labeled as 'non-dippers'. In addition, the duration of sleep for the 'non-dippers' was shorter than the duration for the 'dippers'. The results suggest that there might be an association between aging and duration of sleep, as the older subjects reported reduced sleeping hours in their patient diaries. In a more recent investigation, Dimsdale & Heeren (1998) examined night time blood pressure dipping in twenty-one individuals on two separate occasions (as outpatients and as inpatients). In both instances, they found that night time pressures were significantly lower than day time values with a mean drop for systolic pressure of 9 mm Hg and for diastolic pressure a drop of 8 mm Hg.

Although there is a general consensus that a reduction in blood pressure occurs during sleep, there is a discrepancy as to the degree of nocturnal dipping. Some investigators have suggested that the decrease is as much as 20% (Littler et al., 1975; Littler et al., 1978), others have reported slightly lower values of 10-15% (Broadhurst et al., 1990; Fagher et al., 1995; Schillaci et al., 1996) and still others have reported no drop at all (Harshfield et al., 1993; Fogari et al., 1993; Suzuki et al., 1996). This discrepancy can be attributed in part to the different methods utilized for obtaining blood pressure

values. For example, ambulatory blood pressure monitors, intra-arterial measurements, the auscultatory technique and finger blood pressure devices all offer various degrees of accuracy thereby, minimizing the comparability of values obtained from one method to values obtained from another method. As well, the degree of reduction in pressure could also be affected by the environmental conditions that the subjects were tested in (laboratory versus home), the size of the sample population or any exogenous influences that may not have been equally controlled for by the investigators. It is difficult to precisely determine which factors influence diurnal rhythms in blood pressure since it seems to be affected by many independent factors such as day time activities, duration of sleep, severity of hypertension and aging.

1.6.3 Effects of Hypertension and Aging on Blood Pressure Variability

It has been shown that blood pressure variability increases with the magnitude of the pressure value, as indicated in studies that have examined the day and night patterns of blood pressure in hypertensive individuals (Watson et al., 1980; Drayer et al., 1982; Mancia et al., 1983; Imai et al., 1997). As well, aging is also characterized by a higher systolic pressure and a lower diastolic pressure throughout the day with an increased variability in systolic pressure over a 24 hour period (Drayer et al., 1982; Veerman et al., 1994; Imai et al., 1997). Hypertension and aging are known to cause a decrease in baroreceptor sensitivity (Gribbon et al., 1971; Shimada et al., 1986b; Floras et al., 1988a; O'Rourke, 1990) and thus, the baroreceptors are less responsive and less capable of controlling variations in blood pressure throughout the day.

Shaw et al. (1963) examined the effects of the severity of hypertension on night time reductions by comparing the pattern of blood pressure changes in individuals with either benign or malignant hypertension. They reported that blood pressure decreased during the night in patients with benign hypertension, which is in agreement with the results of earlier work (Brooks & Carroll, 1912), however no such fall was observed in patients with malignant hypertension. Instead, they suggested that the difference might be due to the characteristic pathological changes that occur with malignant hypertension such as stiffening of arterioles and small arteries that produce a relatively 'fixed' vascular resistance. In addition, the investigators reported a greater range for systolic and diastolic pressures in the benign hypertension group over the 24 hour period. Thus, individuals with essential hypertension tend to show increased blood pressure variability.

Like hypertension, aging has also been shown to affect blood pressure variability (Drayer et al., 1982; Mancia et al., 1983; Mann et al., 1985; Floras et al., 1988b). Compared with younger adults, older adults tend to show increased variability in systolic pressure and pulse pressure and a decreased variability in diastolic pressure (Drayer et al., 1982; Imai et al., 1997). Imai et al. (1997) showed an age-dependent increase in blood pressure variability in a study performed on a cohort of northeastern Japanese individuals. Likewise, systolic variability was shown to increase with age ($r = 0.42$, $p < 0.05$) when comparisons were made among 26 patients with ages ranging from 17 to 54 (Watson et al., 1980).

1.6.4 Mechanisms Responsible for Circadian Blood Pressure Variability

The mechanisms responsible for the nocturnal fall in blood pressure are not fully understood. However, it has been suggested that a decrease in blood pressure may be due in part to an increased baroreceptor sensitivity leading to a decrease in sympathetic activity (Smyth et al., 1969; Conway et al., 1983). In normotensive younger adults, the baroreceptors have been shown to play an important role in buffering variations in blood pressure (Conway et al., 1983; Veerman et al., 1994). A decrease in blood pressure and blood pressure variability during the sleeping hours has been shown to be accompanied by an increase in baroreflex sensitivity (Veerman et al., 1994). It has been suggested that during the day, inhibition from higher centers work to operate the baroreceptors. However, during sleep, central inhibition becomes less dominant, thereby increasing the sensitivity of the baroreceptors (Conway et al., 1983). Thus, the baroreceptors play an important part in reducing nocturnal pressure and its variability.

The increased blood pressure variability in hypertensive and elderly subjects may be due in part to the diminished baroreceptor sensitivity that is associated with arterial stiffness caused by hypertension and aging (Roach et al., 1959; Greene et al., 1966; Imai et al., 1997). Gribbon et al. (1971) related baroreceptor sensitivity to age and to high blood pressure in 81 male and female subjects ranging from 19 to 66 years of age. They reported that age was associated with a significant and progressive decline in baroreceptor sensitivity in both normotensive and hypertensive subjects. In addition, baroreceptor sensitivity was also reduced in subjects with hypertension. Furthermore, when a correlation was made between age and level of blood pressure, no statistical

significance was reported, indicating that both factors acted independently on baroreceptor sensitivity. The mechanisms responsible for the diminished sensitivity were not determined in this study. However, other studies have suggested that an alteration in baroreceptor functioning could be the result of a decrease in arterial distensibility that creates an increased stiffness in the arterial walls of both hypertensive and aged subjects (Roach et al., 1959; Mancia et al., 1983; Imai et al., 1997).

A potential mechanism that can decrease blood pressure and its variability during the night is a reduction in sympathetic activity which has been demonstrated in studies observing 24 hour plasma norepinephrine levels (Prinz et al., 1979; Stene et al., 1980; Linsell et al., 1985; Tuck et al., 1985). Tuck and associates (1985) examined the relationship between circadian patterns of arterial pressure and plasma norepinephrine levels in 9 young subjects with essential hypertension and 9 young normotensive subjects. Their results support those of previous studies (Stene et al., 1980; Linsell et al., 1985), that night time blood pressure was lower than day time values. The percent reduction in blood pressure from day to night was greater in the hypertensive group (10.2%) compared with the normotensive group (8.2%) ($p<0.05$). Furthermore, they found that plasma norepinephrine levels were highest in the early morning and decreased throughout the day until reaching its lowest values during the initial hours of sleep. Mean blood pressure values and mean norepinephrine levels were consistently higher in the essential hypertension group compared with the normotensive group during all hours studied. Similar to hypertension, aging has been reportedly associated with elevated plasma norepinephrine levels (Pedersen & Christensen, 1975; Prinz et al., 1979). Prinz et

al. (1979) reported that older subjects exhibited higher plasma norepinephrine levels at all clock times studied and that their night time values exceeded those of younger subjects by 75%.

1.6.5 Summary

Most of the existing literature points to a diurnal variation in blood pressure and its variability in normotension, hypertension and aging. Potential mechanisms responsible for the circadian variation in blood pressure include increased baroreceptor sensitivity and decreased sympathetic activity, represented by reduced plasma norepinephrine levels during the night. In addition, hypertension and aging characteristically show increased blood pressure and blood pressure variability levels throughout the day and night, most likely due to altered cardiovascular variables such as reduced arterial elasticity and increased peripheral vascular resistance. Furthermore, a decrease in baroreceptor sensitivity and an increase in sympathetic activity play contributory roles in maintaining higher blood pressure and blood pressure variability levels in hypertension and aging.

1.7 Methodology: Validity and Reliability

1.7.1 Introduction

Measurement of blood pressure using auscultation at varying intervals throughout the day was the only available method to measure blood pressure variability. Another method that is neither efficient nor economical is to measure blood pressure variability

using an intra-arterial catheter. Perhaps intra-arterial measurement is the most accurate method to measure blood pressure and its variability, however its invasive nature, time inefficiency and cost necessitate the use of other simpler methods.

The FIN.A.PRES (for finger arterial pressure), was introduced in the early 1980's and enabled clinicians to obtain a reliable measurement of beat-to-beat blood pressure noninvasively (Wesseling et al., 1985; Omboni et al., 1993; Imholz et a., 1998). The Finapres device is based on the arterial volume clamp method first developed by Jan Penaz in 1973 (Penaz, 1973). This technique has since been further developed, improved (Wesseling et al., 1982) and clinically tested (Parati et al., 1989; Imholz et al., 1990). Briefly, an inflatable wrap-on finger cuff with a built-in photo-electric plethysmograph is positioned on the middle or index finger and functions against the dynamic (pulsatile) unloading of the finger arterial walls. The equipment includes a servo system and a dynamic servo setpoint adjuster that ensure arterial unloading at zero transmural pressure (Wesseling et al., 1985; Imholz et al., 1998). At zero transmural pressure, the cuff pressure is equal to the intra-arterial pressure, which is determined indirectly by measuring the cuff pressure (Imholz et al., 1988). For a further description of the technique and its major system components, a detailed explanation is found elsewhere (Wesseling et al., 1985). In short, the Finapres apparatus detects a finger pressure waveform and from the waveform, heart beats are detected and systolic, diastolic, mean pressure and pulse pressure are obtained on a beat-to-beat basis (Imholz et al., 1998).

To determine the accuracy and reliability of the Finapres technique, comparison of other invasive and non-invasive methods for estimating arterial pressure have been

performed (Imholz et al., 1988; Parati et al., 1989; Imholz et al., 1990; Bos et al., 1992; Rongen et al., 1995; Ristuccia et al., 1997; Omboni et al., 1998). In most cases, the Finapres offers a reliable non-invasive alternative to, and a high correspondence with, the invasive method of intra-arterial measurements (Parati et al., 1989; Imholz et al., 1990). For example, Parati and associates (1989) performed a direct comparison between finger and intra-arterial blood pressure monitoring during rest and multiple laboratory tests in 24 normotensive and hypertensive subjects. In the resting condition, they reported a strict linear relation between the two methods for systolic and diastolic pressures. In addition, finger and intra-arterial pressures differed only by 2 to 3 mm Hg with the standard deviation of the average difference being approximately 5 mm Hg. Furthermore, the Finapres proved to be accurate even during laboratory testing such as the Valsalva maneuver where blood pressure underwent abrupt and variable changes. Thus, Parati and workers (1989) were reliably able to reproduce intra-arterial patterns of blood pressure using the Finapres device.

1.7.2 Effectiveness of the Finapres Device in Hypertension and Aging

Studies have been performed to determine the effectiveness of the Finapres technique in diagnostic and clinical application for patients with various diseases such as hypertension. Although there is some variability, the Finapres was shown to provide blood pressure values that were fairly close to values obtained intra-arterially (Kurki et al., 1987; Bos et al., 1992; Omboni et al., 1993). For instance, Bos and colleagues (1992) and Omboni and associates (1993) investigated the accuracy of the Finapres device to

measure blood pressure and its variability in hypertensive subjects since they are known to have compromised peripheral vasculature. Both groups of workers reported a reduced accuracy in the precision of the device in that one or both of systolic and diastolic pressures were consistently overestimated or underestimated compared with intra-arterial measurements. Thus, although the Finapres device offers a reliable estimate for blood pressure values, it should be noted that in persons with cardiovascular complications, Finapres measurements do not always equal intra-arterial pressures and hence, accuracy and precision may be compromised.

Aging has also been associated with reduced accuracy in blood pressure values when measurements are made using the Finapres device (Rongen et al., 1995). Rongen et al. (1995) compared blood pressure values measured by the Finapres and intra-arterially in 15 elderly subjects aged 71 to 83 years. Responses were compared in several conditions including supine rest, standing, head-up tilt, Valsalva maneuver and mental arithmetic. They reported that during supine rest, the Finapres significantly underestimated intra-arterial systolic pressure by 16.8 $\pm$ 2.6 mm Hg ($p< 0.001$) and diastolic pressure by 10.8 $\pm$ 1.5 mm Hg ($p< 0.001$). From these results, they suggested that absolute blood pressure levels in the elderly should not be determined by the Finapres. In addition, in response to the orthostatic stress of head-up tilt, systolic blood pressure responses were overestimated by the Finapres. As for the pathologic blood pressure response to standing, the Finapres reliably recorded values in this age group. Thus, depending on the circumstances that blood pressure is being measured (eg. clinical setting versus physiological research) or whether the quantitative or qualitative aspects of

the results are of importance, caution must taken when interpreting the responses. Therefore, it was concluded that the Finapres offers blood pressure values that are similar in appearance and direction but not in magnitude to the values obtained intra-arterially. Furthermore, for qualitative performance, the Finapres proves to be useful in clinical settings however, for physiological research, small quantitative differences between intra-arterial and Finapres responses may be confounding in studies utilizing elderly subjects.

1.7.3 Limitations of Finapres Measurement

Although the Finapres has proven to be a useful, non-invasive technique to measure the variability in blood pressure, there are some important physiological considerations that need to be addressed. Firstly, a difference between the brachial and finger pressure gradient is likely to cause the finger pressure to be different from the pressure in the upper arm. Secondly, the accuracy and precision of the Finapres technique is hampered by factors such as cuff application and the proper selection of fingers. And thirdly, there has been a problem encountered with Finapres blood pressure monitoring over prolonged recording periods.

To address the first issue regarding the pressure gradient, it is obvious that the site of intra-arterial measurement in the brachial artery is more proximal than that of the finger. Because of this, there is a difference in the pressure gradient between the two locations with the mean finger pressure being slightly lower than the brachial pressure (Imholz et al., 1988). Some reports have suggested that the difference in the gradient is approximately 7 to 8 mm Hg (Smith et al., 1985). Also, if blood flow is increased or

arterial vasoconstriction occurs, the brachial to finger pressure gradient rises as occurs during maneuvers like the Valsalva. Moving toward the periphery, the pressure waveform increasingly becomes distorted owing to reflections of the pulse wave. This results in an increased pulse pressure and an overshoot in systolic pressure (Imholz et al., 1988; Rongen et al., 1995). Thus, the brachial to finger pressure gradient is a potentially confounding factor contributing to the variation in pressure values found between intra-arterial and Finapres measurements.

When using the Finapres device, it is of significant importance to select the appropriate cuff size and to ensure proper application of the cuff. Proper positioning of the cuff on a finger can affect the outcome of the results, as was found by Jones et al. (1993) when they noted a decrease in the accuracy of the device when the cuff was loosely applied to the finger. In addition, choosing the appropriate finger for application is also important. Normally, the cuff is applied to the middle or annular fingers. However, sometimes it is necessary to switch sites in order to achieve a finger pressure value that corresponds closely to the auscultatory reference value (Nordin & Fagius, 1995). Thus, by keeping the cuff size and cuff position stable and by keeping the selection of fingers constant, there will be a greater chance of reproducing the blood pressure values.

The last issue that affects the accuracy of the Finapres monitor is when blood pressure is recorded for an extended period of time. Ristuccia et al. (1997) recognized that the Finapres device did not provide accurate estimates of blood pressure during relatively lengthy protocols. They found that during these extended protocols, the finger

pressure did not return to baseline values under normal conditions. However, they found that when the finger was periodically exercised, blood pressure values recovered to initial baseline levels. They suggested that peripheral changes at the finger caused by constant cuff pressure were responsible for the elevations in blood pressure after prolonged measurements. Therefore, in order to prevent the upward drift in blood pressure during protocols of extended duration finger exercise may be beneficial to reduce the constant pressure load on the finger caused by the Finapres.

1.7.4 Summary

Previously, it was only possible to obtain information about blood pressure and blood pressure variability in the presence of an observer. Although the auscultatory technique was useful to evaluate average blood pressure at varying times throughout the day, it was not possible to observe blood pressure changes on a beat-to-beat basis. To accomplish this, intra-arterial recording was necessary, however this invasive procedure is expensive and cannot be used in every situation. Therefore, the development of the Finapres blood pressure monitoring device has proved to be a useful continuous, non-invasive alternative to measure beat-to-beat changes in blood pressure. Its versatility has led to widespread use in clinical application and scientific research because it has been proven to provide accurate estimates of intra-arterial blood pressure. Potential limitations in the accuracy and precision of the device have been observed in patients with compromised peripheral vasculature like hypertension and aging, although it offers qualitatively comparable values. Furthermore, even though the Finapres blood pressure

values have been deemed acceptable in comparison with other methods, certain limitations exist which can potentially lead to inaccurate recordings. These include the brachial to finger pressure gradient, appropriate selection of finger cuff and limitations in the accuracy of blood pressure measurement over prolonged periods of time. Thus, further research and perhaps additional technical advancement is necessary to improve the accuracy and precision of the Finapres device under varying circumstances.

1.8 Exercise Training

1.8.1 Endurance Training Studies

Several investigations have documented the effects of endurance exercise training in hypertension (Cade et al., 1984; Duncan et al., 1985; Hagberg et al., 1983; Hagberg et al., 1989; Ketelhut et al., 1997; Kiyonaga et al., 1985; Seals et al., 1985; Motoyama et al., 1998; Nho et al., 1998). Both epidemiological investigations and longitudinal studies have confirmed the additive benefits of regular physical activity and training. Epidemiological studies have shown that individuals who maintain a physically active lifestyle generally have lower systolic blood pressure and diastolic blood pressure in comparison with their less active, age-matched counterparts (Seals & Hagberg, 1984). Longitudinal training studies conducted in both normotensive and hypertensive subjects have, for the most part, reported significant reductions in blood pressure (Frick et al., 1963; Harris et al., 1967; Seals et al., 1985; Hagberg et al., 1989). However, this finding is by no means universal (Eckblom et al., 1968; Hanson et al., 1968; Blumenthal et al., 1991; Gilders et al., 1989).

The antihypertensive effect of aerobic training has been confirmed in adolescent (Hagberg et al., 1983), middle-aged (Cade et al., 1984; Ketelhut et al., 1997; Nho et al., 1998) and elderly (Seals et al., 1985; Hagberg et al., 1989; Motoyama et al., 1998) populations. There does not seem to be an age-related difference in the magnitude of blood pressure reduction because the changes in blood pressure for adolescent patients and elderly patients have been shown to be similar to those seen in middle-aged patients. Hagberg et al. (1983) studied the effects of exercise training in 25 adolescents (aged 16 ± 1 year) that were persistently above the 95th percentile for blood pressure in their respective age and sex categories. The subjects were encouraged to work towards exercising continuously for 30-40 minutes at an intensity that elicited heart rates equivalent to 60-65% VO_{2max}. The 6-month training period resulted in blood pressure reductions for all hypertensive participants. Mean pressures for the entire group decreased significantly (systolic pressure 137 ± 1 mm Hg to 129 ± 1 mm Hg; diastolic pressure 80 ± 2 mm Hg to 75 ± 2 mm Hg) following the training period.

In a subsequent investigation, Hagberg et al. (1989) studied the effects of a low intensity and a higher intensity exercise prescription in 60 to 69 year old subjects with essential hypertension. The subjects were randomized into one of the following groups: a control group, a low intensity training group or a higher intensity training group. The low intensity exercise group walked at home unsupervised for 1 hour at 50% VO_{2max} and the higher intensity exercise group was required to progress from walking to jogging for 45-60 minutes at a training intensity that was gradually increased to 70-85% VO_{2max}. Both exercise groups trained 3 days a week for a 37 week period. Interestingly, their

results showed that 3 months of low intensity exercise led to significant reductions in blood pressure that were either equal to or greater than those elicited by higher intensity training. Even after 9 months of training, the low intensity group showed further reductions in blood pressure (20/11 mm Hg) that remained greater than those observed for the higher intensity group (8/11 mm Hg). These findings and the results of other investigations concluded that low intensity exercise was as effective as and possibly even more effective than exercise at a higher intensity in reducing blood pressure in hypertensive patients (Matsusaki et al., 1992; Rogers et al., 1996).

While a number of studies have used dynamic exercise such as cycling, walking and jogging which typically involve activity of large muscle groups, no specific guidelines have been designed to promote a maximum reduction in blood pressure. Some investigators have supported the concept of training at a low to moderate intensity (40-60% VO_{2max}) versus a high intensity ($\geq$ 70% VO_{2max}) to elicit a hypotensive training effect (Anderssen et al., 1995; Blumenthal et al., 1991; Hellenius et al., 1993; Okumiya et al., 1996). Gilders et al. (1989) failed to show reductions in blood pressure following a 16 week high intensity training program (70% VO_{2max}) in normotensive and hypertensive subjects. They suggested that perhaps the training intensity was too high to elicit a training response.

Antihypertensive effects of exercise have been shown to occur with training frequencies ranging from two to seven days a week (Cade et al., 1984; Ketelhut et al., 1997; Nho et al., 1998). However, most studies revealed that three days a week provided sufficient stimulus to promote an exercise-induced attenuation in blood pressure

(Hagberg et al., 1983; Hagberg et al., 1989; Motoyama et al., 1998). With respect to the exercise session duration, the range is variable. For instance reductions in blood pressure have been elicited with a training duration of 30-45 minutes per session (Cade et al., 1984), however, training for 50-60 minutes per session has been shown to provide additional benefits (Hagberg et al., 1989; Ketelhut et al., 1997).

Despite the fact that aerobic exercise has been acknowledged for its positive effect on blood pressure, widespread acceptance of its use as a non-pharmacological method to treat hypertension has not been attained. The lack of agreement stems from the existence of methodological flaws in the existing literature. For example, many studies lacked a valid control group thus, there was no way to identify whether the reductions were simply due to environmental factors, the "white coat effect" or due to the actual training stimuli. Also, there were limitations in measuring blood pressure objectively since most studies used standard sphygmomanometry techniques. Finally, some studies did not measure blood pressure in a blinded fashion. When comparing studies that utilized a blind measurement of blood pressure (e.g. automatic blood pressure recorders) with studies that did not (measured blood pressure with auscultation), the studies with blind measurement showed the smallest blood pressure reductions. It is likely that observer bias may have been a confounding factor, therefore, although most studies to date are in agreement with the role of aerobic exercise in attenuating blood pressure, future research should be directed toward better control of these confounding variables.

1.8.2 Resistance Training Studies

Over the past several decades, resistance exercise training has received attention regarding its potential for positive cardiovascular adaptations in normal populations (Wilmore et al., 1978; Gilders et al., 1991; Copeland et al., 1996; McCartney et al., 1996). However, there is limited research pertaining to the use of resistance training in populations with cardiovascular complications or hypertension (Hagberg et al., 1984; Harris & Holly, 1987; McCartney, 1998). This is likely because resistance training has previously been contraindicated for such populations due to the large pressor response evoked by a prolonged isometric contraction (McCartney & McKelvie, 1996). Two main mechanisms are thought to be responsible for the pressor response. These include a central command component and a peripheral control component. The former is primarily responsible for the activation of motor units and the latter is mediated by type III and type IV afferents relaying metabolic changes in the contracting muscles through the spinal cord to the cardiovascular control centers in the brain (Shephard et al., 1981). These central and peripheral components influence heart rate, cardiac output and blood pressure. When the pressor response is elicited, there is a supposed large "pressure load" placed on the heart that is caused by a modest increase in cardiac output with little changes in peripheral vascular resistance (Stewart, 1989), lending to an increase in arterial pressure.

McCartney & McKelvie (1996) have defined resistance training as a combination of static and dynamic contractions. When a muscle initiates a contractile movement, it must first contract isometrically until the muscular force overcomes the resistance of the

object being moved. A dynamic concentric contraction is performed as the weight is raised (e.g. bicep curl), followed by a dynamic eccentric contraction as the weight is lowered. At the end point, the muscle undergoes a relaxation phase between successive lifts (McCartney & McKelvie, 1996).

Heavy dynamic weight lifting in healthy individuals can result in a substantial pressor response, mechanical compression of blood vessels and the use of the Valsalva maneuver, resulting in significant increases in blood pressure (MacDougall et al., 1992). The degree of blood pressure response is usually dependent on the intensity of effort required and not necessarily to the size of the muscle mass involved. In addition, MacDougall and colleagues (1992) showed that the blood pressure response to a leg press exercise in young men with differing quadriceps sizes was similar at the same relative intensity of effort. Furthermore, when the effect of contraction type (concentric versus isometric versus eccentric) was compared at the same relative intensity, the blood pressure response was similar. The investigators concluded that the magnitude of the pressor response was determined by the degree of central command rather than by feedback from group III and IV muscle afferents.

Resistance exercise has been shown to elicit substantial increases in both systolic and diastolic blood pressures with an increase in the magnitude of the blood pressure response occurring with successive repetitions (Haslam et al., 1988; MacDougall et al., 1992; McCartney et al., 1993; Featherstone et al., 1993). This increase in blood pressure response to resistance training has been shown to be similar in magnitude to the responses elicited by heavy aerobic exercise (Wescott & Howes, 1983), but a higher

diastolic pressure may enhance myocardial perfusion by improving coronary artery filling (McCartney, 1998).

Physiological adaptations such as improvements in muscular strength have been observed in middle-aged adults (Wilmore et al., 1978; Harris & Holly; 1987; Gilders et al., 1991; Sale et al., 1994) and elderly individuals (Cononie et al., 1991; Dupler & Cortes, 1993; McCartney et al., 1996; Tsutsumi et al., 1997) following resistance exercise programs. In addition, some training studies have reported increases in muscle cross-sectional area (Wilmore et al., 1978; Gilders et al., 1991; McCartney et al., 1996), increases in lean body mass (Wilmore et al., 1978; Gilders et al., 1991) and decreases in percent body fat (Wilmore et al., 1978; Tsutsumi et al., 1997) following 10 to 20 weeks of resistance exercise. Furthermore, improvements in indices of aerobic capacity such as time to exhaustion on the treadmill have also been reported by some investigators (Wilmore et al., 1978; McCartney et al., 1996).

Circulatory adaptations to resistance exercise include attenuation of blood pressure during contractions performed at the same absolute load (Fleck & Dean, 1987; McCartney et al., 1993; Sale et al., 1994; Copeland et al., 1996). The effect of resistance training on resting blood pressure has not been extensively examined in normal populations or in hypertensive populations. To date, the blood pressure response to resistance exercise is equivocal with some investigators reporting decreases in resting blood pressure (Hagberg et al., 1984; Harris & Holly, 1987; Copeland et al., 1996) while others have found no change (Blumenthal et al., 1991; Cononie et al., 1991; Gilders et al., 1991; Katz & Wilson, 1992; Brilla et al., 1998).

Harris & Holly (1987) examined the effects of weight training in 26 adults with hypertension. Subjects were assigned to either an exercise group or a control group. The exercise group trained 3 days/week for 9 weeks at 40% 1-RM. Following the training period, systolic blood pressure was unchanged, but diastolic blood pressure was significantly decreased by approximately 7%. They suggested that weight training might have a beneficial effect on individuals with borderline hypertension. Similarly, Hagberg et al. (1984) reported that weight training maintained reductions in blood pressure that were previously attained by endurance training in adolescents that underwent 5 months of a resistance training program. Furthermore, they reported that resistance exercise had the potential to further attenuate blood pressure since systolic blood pressure was reduced by an additional 4 mm Hg after weight training.

It seems reasonable to assume that resistance training is not associated with chronic elevations in blood pressure (Hagberg et al., 1984; Cononie et al., 1991; Katz & Wilson, 1992). However, further research is warranted especially in hypertensive populations to determine the effectiveness of resistance training as a non-pharmacological treatment for hypertension.

1.8.3 Isometric Training Studies

1.8.3.1 Factors Involved in Cardiovascular Responses to Isometric Exercise

Isometric exercise training has received limited attention regarding its potential for lowering blood pressure. Because of the large pressor response that occurs during a static contraction (previously described in resistance training section), this form of

exercise training has been contraindicated for individuals with hypertension. In order to understand the potential adaptations associated with isometric training, it is important to review the cardiovascular processes that occur in response to a static contraction. When an isometric contraction is sustained, the intramuscular pressure within the active muscle is increased, which depending upon the length of the contraction and the intensity of the effort, could lead to mechanical hindrance of blood flow (Shepherd et al., 1981). Indirect evidence has suggested that receptors within the muscles are stimulated by chemical changes occurring during the contraction (Shephard et al., 1981). Stimulation of the mechanoreceptors is a potent stimulus for an increased activation of sympathetic nerve activity to human muscle (Mark et al., 1985). Group III and IV muscle afferents respond to these chemical changes by sending impulses to higher cardiovascular centers in the brain. As a result of the impulses directed toward the cardiovascular centers, there is an increase in heart rate due to a decrease in vagal activity to the heart. As heart rate increases, cardiac output also increases and is thought to be responsible for the pressor response. Mechanoreceptors in the carotid sinus and aortic arch are activated in response to the rise in arterial blood pressure and act to modify such an increase.

Recently, the circulatory responses to rhythmic and sustained isometric exercise in normal subjects have been investigated by several researchers (Somers et al., 1992; Joyner & Weiling, 1993; Sinoway et al., 1996; Ferguson & Brown, 1997). By utilizing an exercise duration that modestly, rather than dramatically raises blood pressure, the associated pressor response could be minimized. In addition, by intermittently interrupting the contraction with rest intervals, the isometric effort would elicit lower

elevations in blood pressure. Furthermore, it has been suggested that the rate of rise in blood pressure is proportional to the maximum contraction force (%MVC) and the duration of the contraction, therefore at a moderate intensity (20-35% MVC), the blood pressure response would be less (MacDougall et al., 1985; Wiley et al., 1992). Taken together, a decrease in the magnitude of the rise in arterial pressure during a moderate intensity isometric contraction with brief periods of rest could avoid the potentially dangerous high pressures elicited during higher intensity contractions or during contractions held to fatigue. Avoidance of the large pressor response experienced during an isometric contraction of this nature implicates the potential usefulness of this form of exercise training on blood pressure.

1.8.3.2 Effects of Isometric Training

During the last ten years, there has been a rising interest in the physiological adaptations that result from isometric exercise training (McCoy et al., 1991; Somers et al., 1992; Joyner & Weiling, 1993; Sinoway et al., 1996; Ferguson & Brown, 1997; Kagaya & Homma, 1997; Mostoufi-Moab et al., 1998). Many of the investigations have utilized rhythmic isometric handgrip protocols where contractions are performed with intermittent relaxation periods at training intensities ranging from 25% to 40% MVC (Somers et al., 1992; Wiley et al., 1992; Sinoway et al., 1996; Ferguson & Brown, 1997).

Several physiological adaptations have been reported following 4 to 8 weeks of isometric training including attenuated blood pressure responses to the same absolute

load (Ferguson & Brown, 1997; Mostoufi-Moab et al., 1998), enhanced blood flow to the active muscle (Sinoway et al., 1987; Kagaya & Homma, 1997), reduced muscle sympathetic nerve activity (Somers et al., 1992; Joyner & Weiling, 1993; Sinoway et al., 1996) and decreased resting blood pressure (Wiley et al., 1992).

Somers and colleagues (1992) examined the effects of endurance forearm training on chemoreflex stimulation during exercise. They had subjects perform two 2-minute unilateral isometric handgrip contractions at 33% MVC before and after training. Subjects were required to perform 2 bouts of low resistance (30% MVC) isometric handgrip contractions to fatigue (30 contractions/min.) 5 days a week for 6 weeks. Their results showed significant attenuation of the sympathetic nerve response to endurance forearm training. Despite the reduced sympathetic nerve response there was no accompanying decrease in blood pressure as was expected. The investigators attributed the lack of blood pressure attenuation to the method used to measure blood pressure (sphygmomanometry recordings) and to the power of the investigation (n=5). To corroborate this finding, Sinoway and associates (1996) confirmed the post training attenuation in sympathetic nerve response measured at the peroneal nerve following an intermittent handgrip training protocol at 25% MVC (2 sec on/ 3 sec off) for 30 minutes, performed 5 days a week for 4 weeks.

Mechanisms that have been suggested to explain the decreased sympathetic nerve response following isometric training are related to muscle metaboreceptors, improved vascular capacitance and changes in the ability of muscle to utilize aerobic metabolism more efficiently (Somers et al., 1992; Sinoway et al., 1996). Somers et al. (1992) have

speculated that an improved ability to maintain aerobic metabolism in the trained muscle would result in a decreased need for anaerobic metabolism, thereby, minimizing metabolite accumulation within the muscle which subsequently would lead to a reduced stimulation of chemosensitive receptors.

Although the evidence is limited, exposure to isometric exercise has been shown to attenuate rather than induce high blood pressure responses in normotensive individuals. An important issue to consider is whether isometric exercise would be a safe and effective form of training for individuals with hypertension. Only three studies have been identified that have examined the blood pressure responses to isometric training in hypertension (Kiveloff & Huber, 1971; Buck & Donner, 1985; Wiley et al., 1992). Therefore, further investigations into the effects of isometric training on resting blood pressure are warranted.

In an early investigation, Kiveloff & Huber (1971) suggested that repeated exposure to isometric exercise had the potential to attenuate resting blood pressure. They examined the effects of brief maximal whole body isometric exercise (6 seconds) repeated three times daily for five to eight weeks in individuals with slightly elevated resting blood pressure. Subjects were instructed to contract muscles in their legs, arms and torso so as to sustain a whole body isometric effort. They reported that performance of whole body isometric contractions elicited a hypotensive effect in subjects following training. A potential limitation of the study was the lack of measurement of isometric force because there was no standardization or specialized equipment to measure the force of the contraction. This would make it difficult to quantify the true training effects. The

study did however, provide a novel insight into the potential for isometric exercise to lower blood pressure. To corroborate this training effect, Buck & Donner (1985) provided comparable evidence reporting that the incidence of hypertension varied according to the quantity of isometric exercise associated with various occupations. Seventeen hypertensive men participated in the investigation. Each subject was classified according to the level of isometric stress (low versus moderate versus high) related to their occupation. The investigators found that the incidence of hypertension was higher in professions with low isometric stress compared to those with moderate-high isometric stress. They concluded that continued exposure to isometric exercise prevented rather than induced hypertension.

The most recent evidence suggesting that isometric exercise lowers resting blood pressure was provided by Wiley and colleagues (1992). They conducted two controlled studies that documented the positive effects of isometric exercise on resting blood pressure. In the first study, subjects with high-normal resting diastolic pressure performed four 2-minute contractions with 3-minute rest intervals between contractions, 3 days a week for 8 weeks. Contractions were performed at 30% MVC. Their results indicated that a significant decline in both systolic and diastolic resting blood pressure occurred following training, with no change in resting blood pressure of matched controls. The results of the second study showed that subjects with borderline hypertension also benefited from isometric training. This protocol required subjects to perform four contractions at 50% MVC for 45-seconds with 1-minute rest intervals between contractions, 5 days a week for 5 weeks. Training resulted in significant

reductions in resting systolic and diastolic pressure. In addition, with cessation of training, it was noted that blood pressure returned to its pre-training value over a similar time course. Thus, Wiley and associates (1992) showed that isometric training at a moderate intensity, one that does not elicit a high pressor response, was adequate to attenuate resting pressure in hypertensive individuals.

Potential mechanisms associated with the attenuated blood pressure response following isometric training have been proposed but not thoroughly investigated (Wiley et al., 1992). These include alterations in cardiac output, total peripheral resistance or modulation of the autonomic nervous system. In addition, repeated exposure to the pressor response might act as a stimulus to reset the baroreceptors. The exact mechanisms related to the reduction in blood pressure following prolonged exposure to isometric exercise have not been investigated. This lack of evidence warrants further research in this area.

1.9 Statement of Purpose

The purpose of this thesis investigation was to examine the effects of 10-weeks of isometric training on resting blood pressure in older adults with hypertension and to establish potential mechanisms that might explain the altered blood pressure response. Power spectral analysis of heart rate variability and blood pressure variability was used to assess modulation of the specific branches of the autonomic nervous system between two groups of older adults with hypertension. Subjects were randomized to a training (n=9) group consisting of isometric handgrip exercise and a control (n=8) group. The

hypotheses were that isometric handgrip training would: 1) attenuate resting blood pressure; 2) decrease sympathetic modulation of heart rate; and/or 3) increase parasympathetic modulation of heart rate.

2.0 METHODS

2.1 Subjects – Recruitment & Screening

Seventeen hypertensive men and women (10 Males and 7 females) ranging in age between 60 and 80 years (mean age 67.5 years) volunteered to participate in this investigation. Nine participants served as subjects in the isometric training group (5 males, 4 females) and 8 participants comprised the control group (5 males, 3 females). All were healthy, active and had no previous experience with isometric handgrip training or any form of isometric exercise. The control group underwent weekly blood pressure measurements but were not required to train. Subjects were recruited from the McMaster University Seniors Exercise Program and all subjects had been members of the program for a minimum period of 2.5 years. Participants were initially contacted by phone or at the exercise facility regarding the purpose and procedures involved in the study. The investigation required that all subjects were in a good general state of health and had a seated resting systolic blood pressure that was greater than or equal to 140 mm Hg and/or a diastolic pressure greater than or equal to 85 mm Hg. Individuals with blood pressure values in this range were considered as borderline to mildly hypertense (Tipton, 1991). Subjects taking antihypertensive medication prior to the initiation of the study were

included in the sample population since all subjects had been on the medication for 5 years or longer.

All subjects were tested in the Cardiac Rehabilitation laboratory at the McMaster University Ivor Wynne Center. Initial screening required that subjects come into the lab one week prior to the first week of training in order to obtain baseline blood pressure values. The purpose of the screening visit was to allow a more detailed disclosure of the study protocol, purpose and time commitment as well as to determine if subjects met the inclusion criteria. Informed consent was obtained from all participants prior to beginning any testing procedures. This investigation was approved by the University's Human Ethics Committee.

2.1.1 Subject Demographics

A one-way ANOVA was performed on baseline subject characteristics and revealed that training subjects were similar to control subjects with respect to age, height, weight, baseline resting blood pressure, exercise program duration and number of years taking anti-hypertension medication. Refer to Table 1 for further details concerning subject characteristics.

2.2 Experimental Design

Isometric handgrip training was performed 3 days a week for 10 weeks. Subjects came into the lab at the same time of the day for each training session. A computerized handgrip (IBX-H101, powered with a 9VDC battery) dynamometer recorded maximum

handgrip tensions by way of two electronic load cells located in the device to measure applied forces. Subjects viewed their maximum voluntary contractions (in pounds) on a display screen built into the device where a bar-graph indicated the amount of force production as the handle was being squeezed. After the maximal isometric force was determined for the right hand, a one-minute period of rest was taken prior to determining the maximal isometric force for the left hand.

Table 1: Subject Characteristics for Training and Control Group

Demographic	Training (n=9)	Control (n=8)
Age (years)	69.3 ± 6.0	64.2 ± 5.5
Gender	5 male, 4 female	5 male, 3 female
Height (cm)	162 ±15.0	162 ± 9.0
Weight (kg)	77.5 ± 15.8	88.9 ± 9.6
Resting SBP (mm Hg) Resting DBP (mm Hg)	156.0 ± 9.4 82.3 ± 9.3	152.0 ± 7.8 87.1 ± 10.8
Exercise Program Participation (years)	4.0 ± 2.9	2.0 ± 1.4
Medication (years)	9.4 ± 11.8	9.2 ± 10.6

On the third training day of each week, subjects were asked to come into the lab and sit quietly in a relaxed state for at least 10 minutes so that seated resting blood pressure measurements could be taken. Blood pressure was measured in the left arm of each subject, three times with one minute separating each reading and the average of the

three values was determined. Blood pressure was measured indirectly by auscultation using a standard sphygmomanometer. For the entire duration of the study, blood pressure measurement was taken by only one experimenter. The exercise program was scheduled for 3 days a week for a 10 week duration. Any subject that could not complete all 30 sessions would be discontinued from the study.

2.2.1 Training Intervention

The training protocol consisted of four two-minute isometric contractions at 30% of maximal strength, using alternate hands. Subjects had a one-minute rest period between each contraction. This protocol was chosen based on a previous study (Wiley et al., 1992) in which contractions held at submaximal levels elicited a training response. Subjects viewed their isometric force production on the display screen where an arrow indicated the target force of 30% MVC. Subjects were verbally encouraged to maintain their force production as close to the arrow as possible until the count-down timer had expired (equivalent to two minutes). In addition, the IBX-H101 computer evaluated how well each subject adhered to the prescribed effort on a scale of 0 to 100 with 100 being a perfect score.

2.2.2 Heart Rate Variability Techniques

2.2.2.1 Frequency Domain Analysis of Heart Rate Variability

2.2.2.2 Protocol and Signal Processing

The power spectral analysis of HRV was performed in a laboratory room at the Ivor Wynne Center. HRV of all subjects was recorded in three conditions at baseline, at week five and at week ten. The conditions were as follows: 1) during 10-minutes of supine rest; 2) during 5-minutes of upright sitting; and 3) during 10-minutes of standing. The supine and standing recordings were taken to provide an estimate of sympathovagal balance in the resting state. In addition, the supine and standing values at baseline were compared with mid and post-training recordings in order to assess any changes in autonomic modulation resulting from the 10 week isometric handgrip training regimen. The upright sitting recordings were taken to obtain the average resting blood pressure of each subject over the 5-minute period, therefore HRV was not assessed in the sitting condition.

Before the HRV power spectral monitoring was initiated, subjects were asked to remove or manipulate their upper body garments in order to apply the monitoring electrodes. The HRV monitoring took place in a small room located inside the Cardiac Exercise Rehabilitation Laboratory at the Ivor Wynne Center at McMaster University. The testing room was quiet and maintained at a constant temperature of 18 to 20°C to ensure subject comfort during the recording period. Subjects assumed a supine position on the laboratory bed and were encouraged to remain quiet, relaxed and awake during the

recording period. The skin was prepared in six locations on the chest by cleansing the skin with an alcohol preparation. Lead placement for all three conditions remained unchanged, consisting of a bipolar II arrangement. In placing the three ECG electrodes, care was taken to avoid DC interference so that R-wave signals would be clean for data processing. In addition, three electrodes were attached to the chest to simultaneously record the respiratory signal. Previous observation of the effects of respiratory sinus arrhythmia (RSA) on HRV made it essential for respiratory frequency to be monitored, in conjunction with heart rate (Saul et al., 1989; Malliani et al., 1991; Brown et al., 1993).

Each of the ECG, blood pressure and respiration signals were sampled at 500 samples/second using a 12 bit analog-to-digital converter [CODAS, DATAQ Inc, Ohio, USA]. The signals were continuously displayed on a 486 IBM laptop computer using WINDAQ data acquisition software. Adjustments were made to the sensitivity of the ECG signal prior to the recording in order to maximize the resolution of the successive R-R intervals. Three channels were displayed simultaneously using WINDAQ data acquisition software and the data were saved on the hard-drive.

2.2.3 Blood Pressure Variability Technique

Continuous beat-to-beat blood pressure recordings were obtained from the subject's middle finger of the non-dominant hand by photoplethysmography (Finapres blood pressure monitor, Ohmeda 2300), while the hand rested at heart level. Care was taken to fit the subject's finger with the appropriate cuff size in order to maximize recording accuracy. Occasionally, the cuff had to be repositioned or replaced with a

different cuff when the characteristic shape of the blood pressure wave was not optimal. To reposition the cuff, the Finapres was turned off and the cuff was removed from the finger and repositioned on the same finger. Once an adequate blood pressure signal was established, the size of the finger cuff was recorded and the same cuff was used for all three recording conditions and subsequent recordings at week 5 and week 10. The Finapres was calibrated to a mercury monometer and the same reference file was used for each recording. The Finapres was turned on approximately 5 minutes before data acquisition was initiated so that an accurate blood pressure wave could be established. The Finapres device has a servo-self adjust feature that can be used to automatically reset the blood pressure waveform intermittently throughout the recording period. When the servo-self adjust option was set, the pressure in the bladder of the finger cuff was released and recalibrated every 30-45 seconds to avoid movement of the waveform from baseline. This function helped to improve the accuracy of the recording. In order to analyze the blood pressure data using power spectral analysis, the servo-self adjust function was turned off for the duration of the recording to avoid continuous intermittent pauses in the data. With the servo-self adjust function off, the quality of the waveform was optimal but quantitatively the absolute values for systolic and diastolic pressure may have been less accurate. Therefore, the Finapres data was used to obtain low frequency and high frequency components of blood pressure variability and not used to determine absolute blood pressure values.

Supine Condition

Patients were asked to refrain from making any abrupt movements, to relax as much as possible without falling asleep, not to talk and to keep deep respiratory movements to a minimum. These requests were made in order to minimize movement artifact upon the ECG signal as well as to minimize RSA effects due to talking. Blood pressure was recorded via the Finapres as the non-dominant hand was comfortably positioned at the subjects side, resting at heart level on the bed in which they were lying.

Sitting Condition

Following the supine condition the Finapres was turned off to allow the subject's finger to relax. Subjects were asked to sit up slowly and upon their readiness to move into the sitting condition. Once again, when the subject was ready, the Finapres was turned on and they were asked to remain relaxed and quiet for the 5 minute duration of the recording. Subjects sat comfortably in a chair with the Finapres arm resting on the bed adjacent to them in order to keep the arm maintained at heart level. After the sitting recording, the Finapres was again turned off and blood pressure was measured by means of auscultation and sphygmomanometry. Three values for systolic and diastolic blood pressure were obtained with one minute separating each measurement. The mean of the three values was taken as the average resting seated blood pressure for that session.

Standing Condition

Following the sitting condition, subjects were asked to stand assuming a relaxed stance. Again, heart rate, respiration and blood pressure were recorded for 10 minutes and subjects were asked to refrain from making any abrupt movements in their posture.

Subjects were encouraged to stand with their arm relaxing on a cardboard box that was positioned on top of the bed adjacent to them, again so the hand would be at heart level. Once the recording was completed, the Finapres was turned off and removed from the subjects finger and the subject was disconnected from the ECG and respiration monitoring devices.

2.2.4 Power Spectral Analysis

Power spectral analysis of heart rate variability was performed on all Windaq raw data files. Files were backed up on Zip disk and transferred to a Pentium computer at Chedoke-McMaster Hospital for power spectral analysis of HRV using MATLAB software. Each of the ECG files recorded during the supine position (lasting 10 minutes) and the standing position (lasting 10 minutes) for each subject (at baseline, week 5 and week 10) were analyzed using HRV power spectral computational software. An RR-interval tachogram was formed from the continuous ECG data using a QRS detection algorithm. Then the RR tachogram was inspected for ectopic beats. If any ectopic beats were present, they were corrected using a linear interpolation algorithm (Kamath & Fallen, 1995). Those patient files that contained several ectopic beats were eliminated from the analysis, unless a sufficiently long portion (3 minutes minimum) of the ECG recording was ectopic free and could be analyzed in isolation. A total of 2 subjects from the control group were excluded from statistical analysis because of excessive ectopic beats (> 5/minute).

At baseline, week 5 and week 10, HRV and BPV in the hypertensive subjects were assessed through changes in the power spectral indices from the 10-minute supine condition and the 10-minute standing condition. It was hypothesized that following training the heart rate variability response in the training group would be altered, while no change would be observed in the control group. Because individuals with hypertension tend to have an elevated LF component and a diminished HF component at rest compared with healthy normotensive individuals, the expected change following training would be demonstrated by: 1) a decrease in the LF component; 2) an increase in the HF component; and, 3) a decrease in the LF:HF ratio. These changes were assessed through comparison of only the baseline and week ten data in order to assess the pre- and post- effects of the training intervention.

The baseline 10-minute supine power spectral recordings were compared with the week 10 (post-exercise) 10-minute supine recordings to assess the effects that isometric training might have on altering the frequency indices of HRV and BPV, thereby indicating changes in autonomic modulation of heart rate. The power spectrum of HRV provided a total of 4 dependent variables for heart rate variability and 6 dependent variables for blood pressure variability. Heart rate variability indices included 1) average heart rate (HR); 2) low-frequency area (LF); 3) high-frequency area (HF); and, 4) LF:HF area ratio. For blood pressure variability, the indices were: 1) systolic blood pressure low-frequency area (SBP LF); 2) systolic blood pressure high-frequency area (SBP HF); 3) systolic blood pressure LF:HF area (SBP LF:HF); 4) diastolic blood pressure low-frequency area (DBP LF); 5) diastolic blood pressure high-frequency area

(DBP HF); and, 6) diastolic blood pressure LF:HF are (DBP LF:HF). Statistical analysis for each index was performed using a one-way ANOVA (GROUP X TIME) on the aforementioned 10 dependent variables for heart rate variability and blood pressure variability.

Since the mean value of heart rate does not contribute to the power spectral information, it was subtracted from the signal. Equally sampled HRV signals were generated using linear interpolation. The signal was then filtered through a second order high-pass Butterworth filter that had a cut-off value of 0.02 Hz. A ninth order autoregressive (AR) model was subsequently applied (Kay and Marple, 1981) with the mathematical expression of the AR model defined below:

$$X[n] = - \sum_{k=1}^{p} a[k] \times [n-k] + u[n]$$

where X[n] represents the output signal at any time point 'n' obtained from the input signal of white noise u[n] and k = {1,2... p} represents the parameters used to describe the signal. To calculate the AR power spectrum, the below parameters are used:

$$P_{AR}(f) = \frac{\sigma^2 \Delta t}{\left[1 + \sum_{k=1}^{p} a[k] \exp(-j2\pi fk\Delta t)\right]^2}$$

where σ^2 is used to represent the variance of the white noise input signal and Δt is used to represent the sampling interval. For a more detailed description of the algorithm used to estimate AR parameters, please see the review by Kay and Marple, 1981.

This procedure was used to determine power spectral measures including low frequency (0.02-0.15 Hz), high frequency (0.15-0.5 Hz) and low frequency to high frequency area ratio for the heart rate and blood pressure variability recordings for each subject.

2.2.5 Statistical Analysis

All descriptive data are presented as means, standard deviations and standard errors (X ± S.E.M). Differences in resting auscultatory blood pressure between the experimental and control groups were determined using a two-way analysis of variance (ANOVA) with repeated measures. *Group*, a between subjects factor with two levels (training and control group), was the first independent variable. The second independent variable was *time*, a within subjects factor with eleven levels (baseline, week 1 to week 10).

A two-way ANOVA with repeated measures was used to compare blood pressure variability (Finapres) data. The first independent variable was *group* with two levels (training and control group), and the second independent variable was *test time/condition* with two levels (baseline and week 10).

A two-way ANOVA with repeated measures was used to compare heart rate variability data. Again, *group* was the first independent variable with two levels (training and control group) and *test time/condition* was the second variable with two levels (baseline and week 10).

A Tukeys Honestly Significant Difference (HSD) post hoc analysis was used to determine specific differences between the groups. An alpha level of <0.05 was considered to be statistically significant. The dependent variables were absolute and relative systolic pressure, diastolic pressure and mean arterial pressure. In addition, resting heart rate, HRV LF area, HF area, LF:HF area ratio and BPV LF area HF area and LF:HF area ratio were also measured.

3.0 RESULTS

3.2 Effects of Exercise Training on Resting Blood Pressure

3.2.1 Absolute Change

Systolic Blood Pressure (SBP)

Statistical analysis of SBP using a two-way ANOVA was performed and revealed a main effect for TIME ($F(10, 150)=4.58$; $p<0.00001$) as well as a significant GROUP X TIME interaction, $F(10, 150)=3.38$; $p<0.0005$. SBP decreased as a result of training in the training group (156 ± 9.4 mm Hg to 137 ± 7.8 mm Hg) versus the control group (152 ± 7.8 mm Hg to 144 ± 11.8 mm Hg) ($p<0.0005$) (see Figure 1). Post hoc analysis showed a difference between groups at week eight and a difference from week one for the training group at week six, week seven, week eight, week ten and week eleven.

Diastolic Blood Pressure (DBP)

As demonstrated in Figure 2, a two-way ANOVA performed on DBP showed a trend toward a reduction in the training group (82 ± 9.3 mm Hg to 75 ± 10.9 mm Hg) compared to the control group (87 ± 10.8 mm Hg to 84 ± 9.6 mm Hg), although, the reduction was statistically non-significant.

Mean Arterial Pressure (MAP)

A two-way ANOVA on MAP values revealed a main effect for TIME ($F(10, 150)=3.21$; $p<0.0009$) and a significant GROUP X TIME interaction ($F(10, 150)=2.13$; $p<0.025$). The attenuated MAP response can be seen in Figure 3, where the training group showed an 11 Torr reduction (107 ± 8.53 mm Hg to 96 ± 8.7 mm Hg) versus a 5 Torr reduction in the control group (109 ± 9.1 mm Hg to 104 ± 9.3 mm Hg) following training. Post hoc analysis confirmed differences between groups at week five, week eight and week ten. As well, a significant difference from week one for the training group was observed at week eight and week eleven.

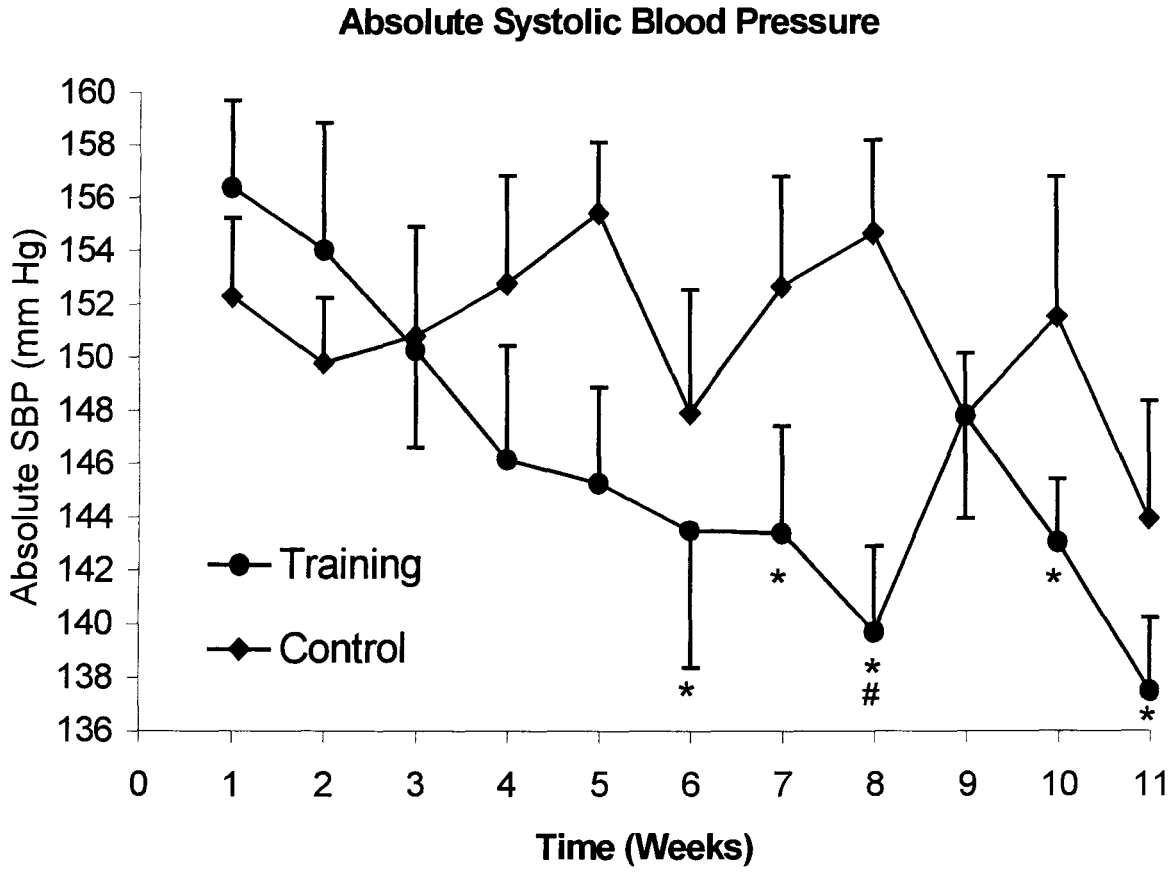

Figure 1. Absolute systolic blood pressure responses by isometric exercise trained (n=9) group and control (n=8) group. Blood pressure values are shown as means (± SE) from the initial measurements (week 1) and the 10 weeks of training. Systolic pressure values for the trained group significantly ($p<0.05$) decreased while the control group did not. Asterisks (*) denote weekly averages significantly different from week 1 for that group and (#) denotes significant differences between groups.

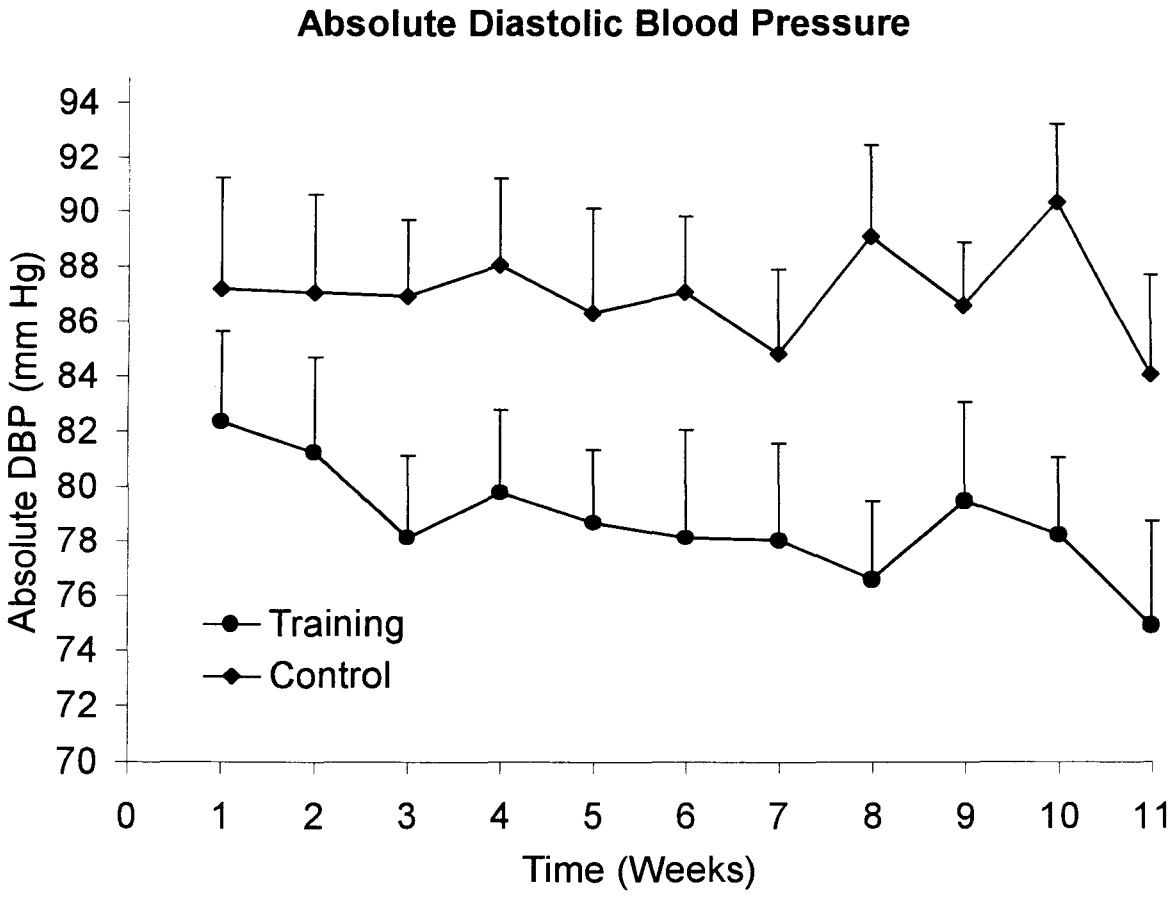

Figure 2. Absolute diastolic blood pressure responses by isometric exercise trained (n=9) group and control (n=8) group. Blood pressure values are shown as means (± SE) from the initial measurements (week 1) and the 10 weeks of training.

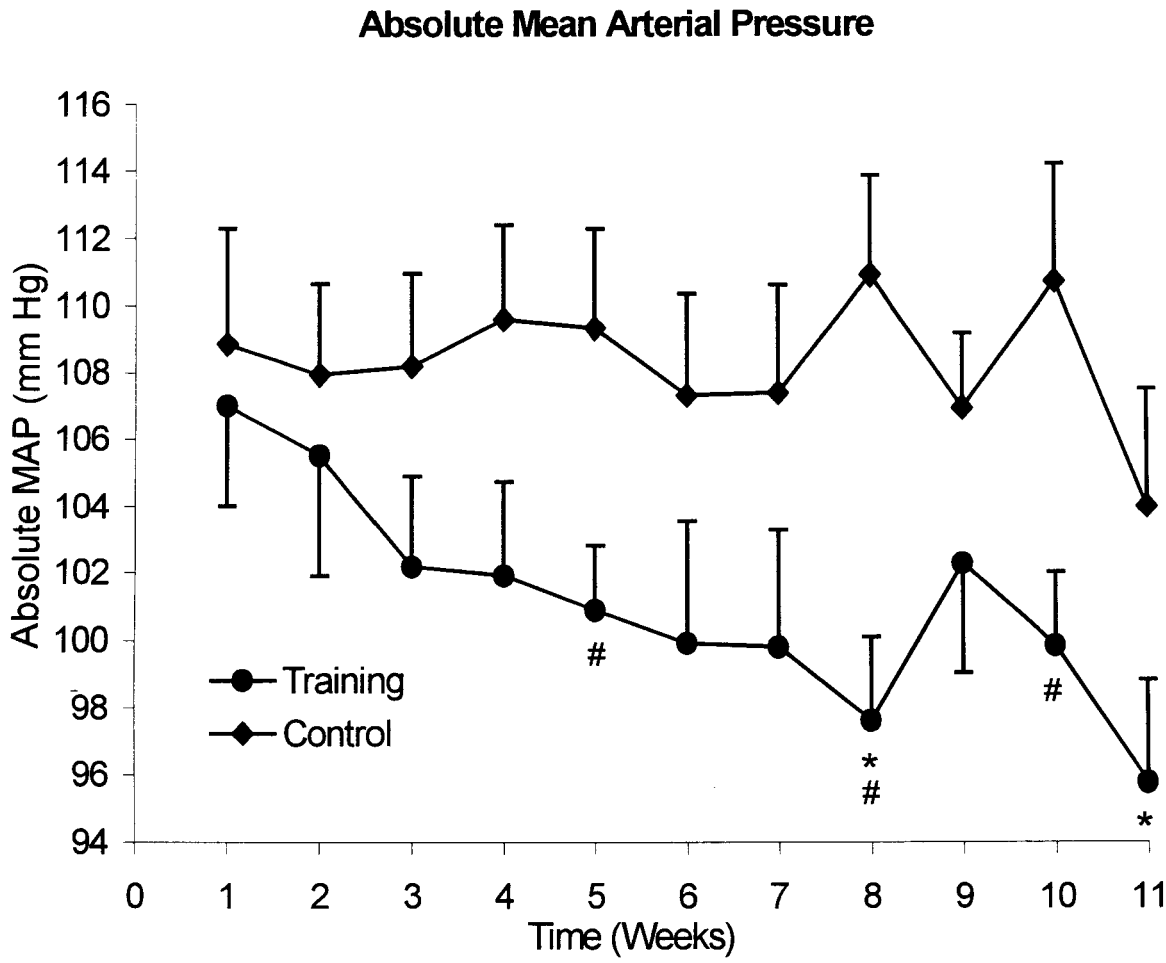

Figure 3. Absolute mean arterial blood pressure responses by isometric exercise trained (n=9) group and control (n=8) group. Blood pressure values are shown as means (± SE) from the initial measurements (week 1) and the 10 weeks of training. Mean arterial pressure values for the trained group significantly ($p<0.05$) decreased while the control group did not. Asterisks (*) denote weekly averages significantly different from week 1 for that group and (#) denotes significant differences between groups.

3.2.2 Relative Change

Systolic Blood Pressure

A two-way ANOVA was performed on the relative change in resting SBP and revealed a main effect for GROUP ($F(1, 15)=7.39$; $p<0.016$), a main effect for TIME ($F(9, 135)=3.69$; $p<0.0004$) and a significant GROUP X TIME interaction ($F(1, 135)=2.92$; $p<0.003$). As demonstrated in Figure 4, the training group decreased their SBP by approximately 12 ± 0.05%. Alternatively, the control group showed only a 5.5 ± 0.06% reduction. Tukey's post hoc procedure identified significant differences between groups at week four, week six, week seven and week nine and significant differences from baseline for the training group at week seven and week ten.

Diastolic Blood Pressure

Values for DBP over the training duration were analyzed using a two-way ANOVA. Although analysis revealed an 8.8 ± 0.1% decrease in the training group versus a 3.3 ± 0.06% decline in the control group, the difference was non-significant (see Figure 5).

Mean Arterial Pressure

A two-way ANOVA for MAP revealed a main effect for GROUP ($F(1, 15)=4.60$; $p<0.049$) and a main effect for TIME ($F(9, 135)=2.92$; $p<0.004$). As demonstrated in Figure 6, a 10.3 ± 0.07% reduction in MAP was observed for the training group compared to a 4.4 ± 0.05% decrease for the control group, however, the reduction was non-significant.

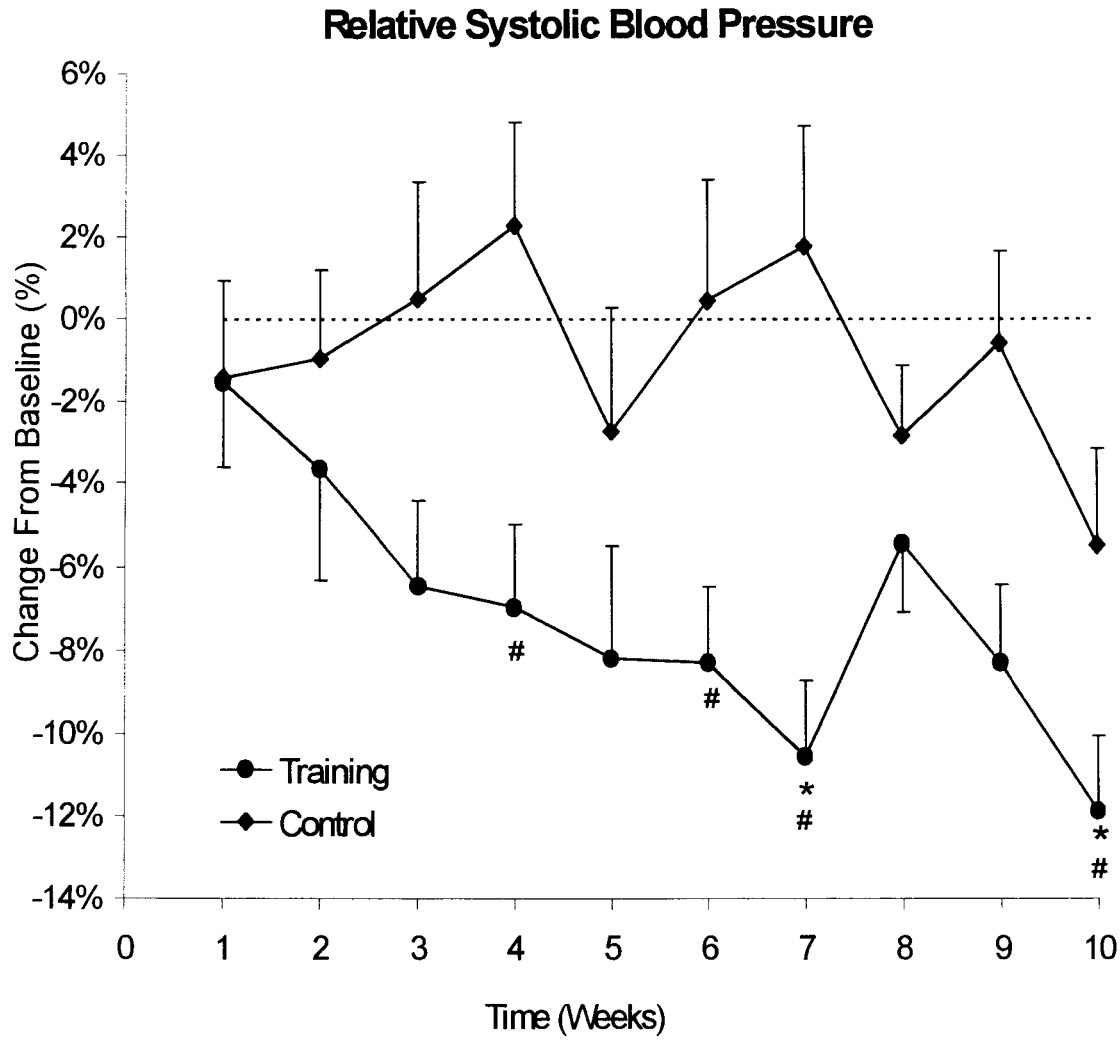

Figure 4. Relative systolic blood pressure responses by isometric exercise trained (n=9) group and control (n=8) group. Blood pressure values are shown as percentages (± SE) to express the change in pressure from baseline (week 0). Relative systolic pressure values for the trained group significantly ($p<0.05$) decreased while the control group did not. Asterisks (*) denote weekly averages significantly different from week 0 and (#) denotes significant differences between groups.

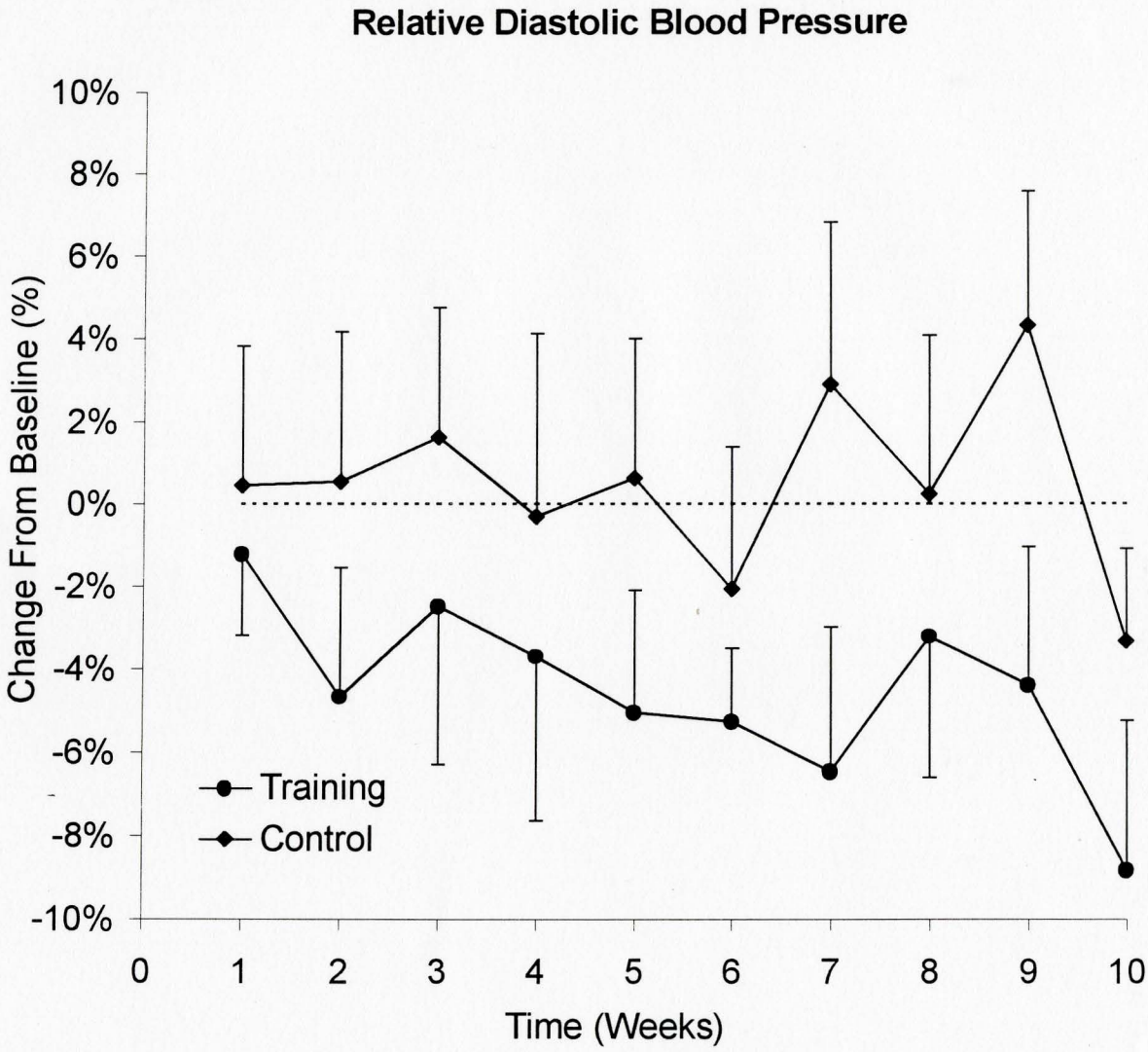

Figure 5. Relative diastolic blood pressure responses by isometric exercise trained (n=9) group and control (n=8) group. Blood pressure values are shown as percentages (± SE) to express the change in pressure from baseline (week 0).

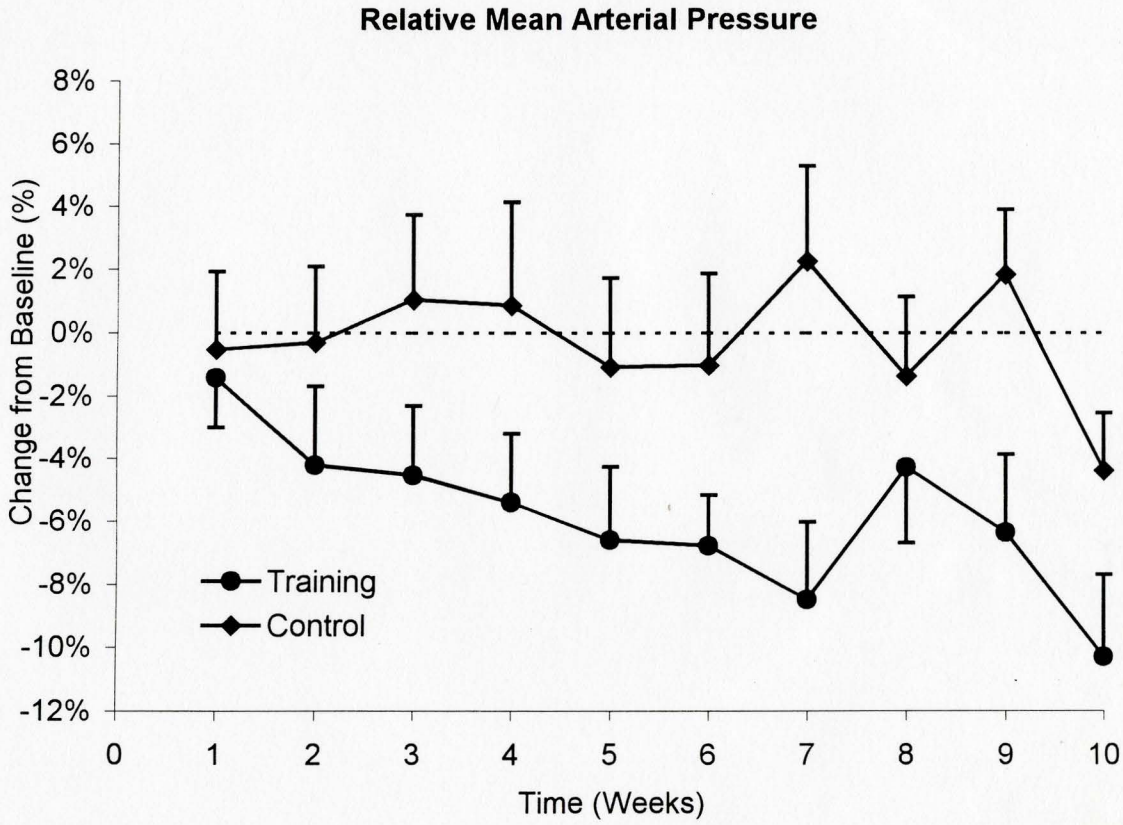

Figure 6. Relative mean arterial blood pressure responses by isometric exercise trained (n=9) group and control (n=8) group. Blood pressure values are shown as percentages (± SE) to express the change in pressure from baseline (week 0).

3.3 Effect of Exercise on Heart Rate and Blood Pressure Variability

Analysis of resting heart rate revealed a significant GROUP X TIME interaction ($F(2,26)=3.65$; $p<0.04$). The training group showed a 2 beat/minute (beats/min) reduction in resting heart rate following training (70 ± 14.2 to 68 ± 12.1 beats/min). Alternatively, there was a 6 beats/min rise in resting heart rate for the control group (70 ± 8.5 to 76 ± 15.3 beats/min.) (see Figure 7).

Statistical analysis of the LF area revealed a main effect for TIME ($F(1,13)=4.79$; $p<0.05$) and a non-significant trend toward a reduction for the training group (6150.34 ± 1002.2 $(beats/min)^2/Hz$ to 5009.62 ± 1506.5 $(beats/min)^2/Hz$) versus (5796.63 ± 731.16 $(beats/min)^2/Hz$ to 5252.8 ± 1195.25 $(beats/min)^2/Hz$) for the control group (see Figure 8). Analysis of the HF area demonstrated a significant GROUP X TIME interaction, as is illustrated in Figure 9, $F(1,13)=15.02$; $p<0.002$. The training group showed an increase in HF area following training (4957.97 ± 1679.7 $(beats/min)^2/Hz$ to 5774.74 ± 1661.51 $(beats/min)^2/Hz$) while the control group showed a change in the opposite direction (5229.71 ± 1735.95 $(beats/min)^2/Hz$ to 4848.95 ± 1342.44 $(beats/min)^2/Hz$). Although there was a trend toward a reduction in the LF:HF area ratio, it did not reach statistical significance (training = 2.16 ± 1.91 $(beats/min)^2/Hz$ to 0.98 ± 0.51 $(beats/min)^2/Hz$; control = 1.31 ± 0.68 $(beats/min)^2/Hz$ to 1.25 ± 0.64 $(beats/min)^2/Hz$) (see Figure 10).

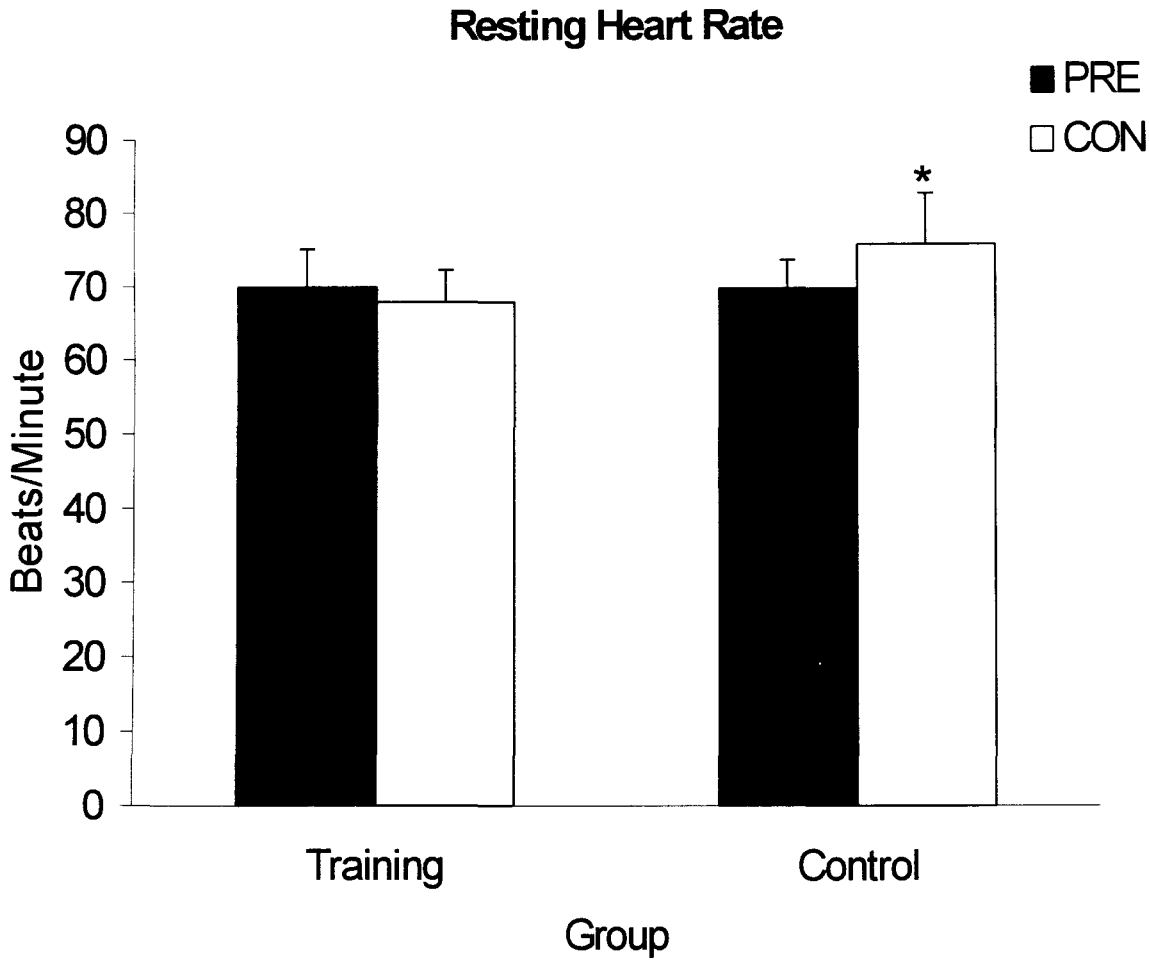

Figure 7. Resting heart rate responses for isometric exercise trained (n=9) group and control (n=8) group. Heart rate values are shown as means (± SE) compared at week 0 and week 10. Heart rate values for the control group significantly ($p<0.05$) increased. Asterisks (*) denote significant differences from week 0.

Based on the blood pressure variability data, analysis of SBP revealed a main effect for TIME for both the LF area ($F(1,13)=10.87$; $p<0.006$) and HF area ($F(1,13)=5.45$; $p<0.04$). In addition, a significant GROUP X TIME interaction was observed for LF area ($F(1,13)=7.17$; $p<0.02$), HF area ($F(1,13)=9.37$; $p<0.009$) and LF:HF area ratio ($F(1,13)=8.05$; $p<0.01$). LF area decreased significantly in the training group 221.06 ± 12.85 $(beats/min)^2/Hz$ to 157.72 ± 36.4 $(beats/min)^2/Hz$ with only a slight change in the control group from 176.13 ± 69.3 $(beats/min)^2/Hz$ to 169.58 ± 63.7 $(beats/min)^2/Hz$, (see Figure 11). As well, there was a significant increase in the HF area for the training group from 33.56 ± 12.04 $(beats/min)^2/Hz$ to 83.07 ± 25.21 $(beats/min)^2/Hz$ while the control group showed only a modest reduction from 92.08 ± 58.35 $(beats/min)^2/Hz$ to 85.40 ± 60.12 $(beats/min)^2/Hz$ (see Figure 12). These changes led to a corresponding decrease in the LF:HF area ratio for the training group (9.22 ± 4.17 $(beats/min)^2/Hz$ to 2.92 ± 2.08 $(beats/min)^2/Hz$) while the control group showed a change in the opposite direction (3.52 ± 2.40 $(beats/min)^2/Hz$ to 6.58 ± 6.41 $(beats/min)^2/Hz$) (see Figure 13).

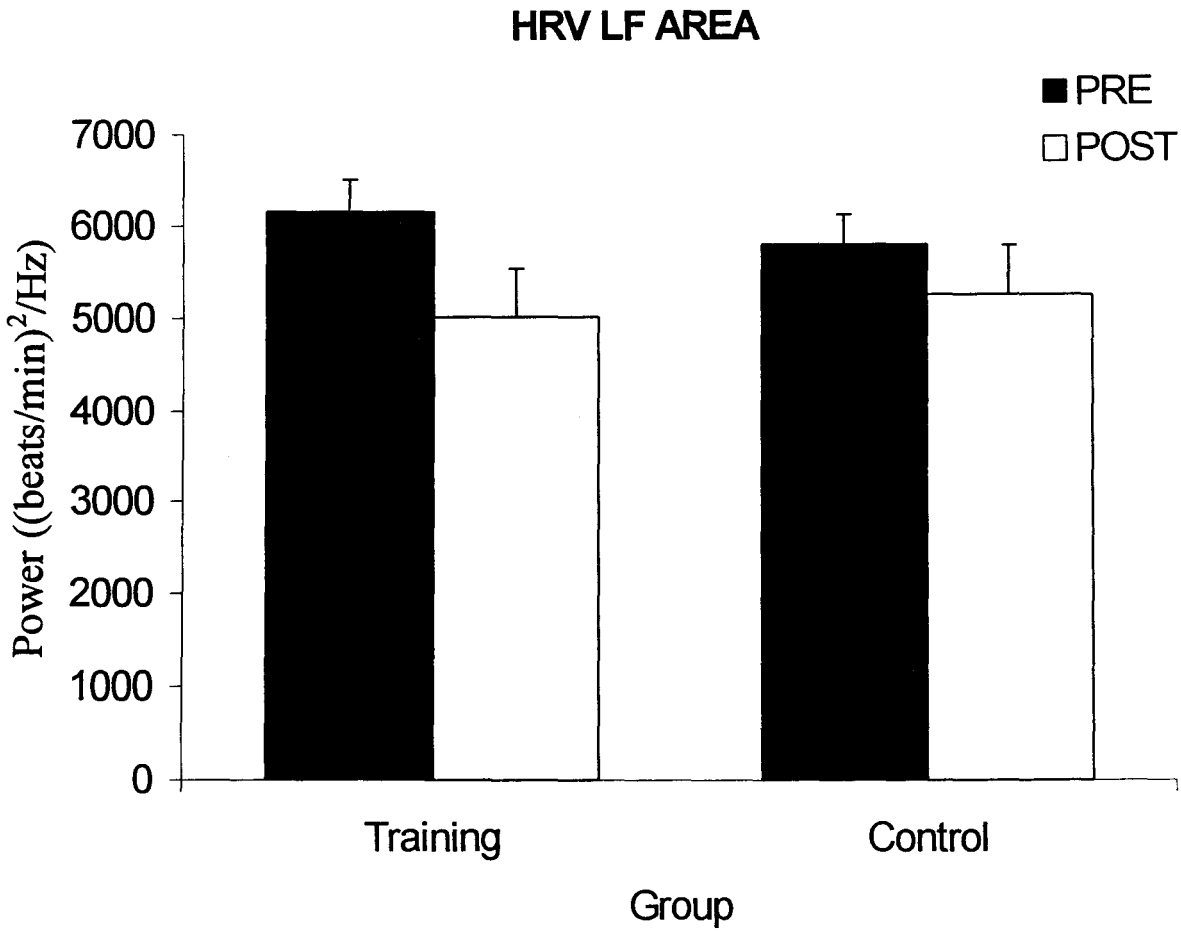

Figure 8. Low frequency area of heart rate variability for isometric exercise trained (n=9) group and control (n=6) group. Values are expressed as means (± SE) and represent week 0 and week 10 measurements.

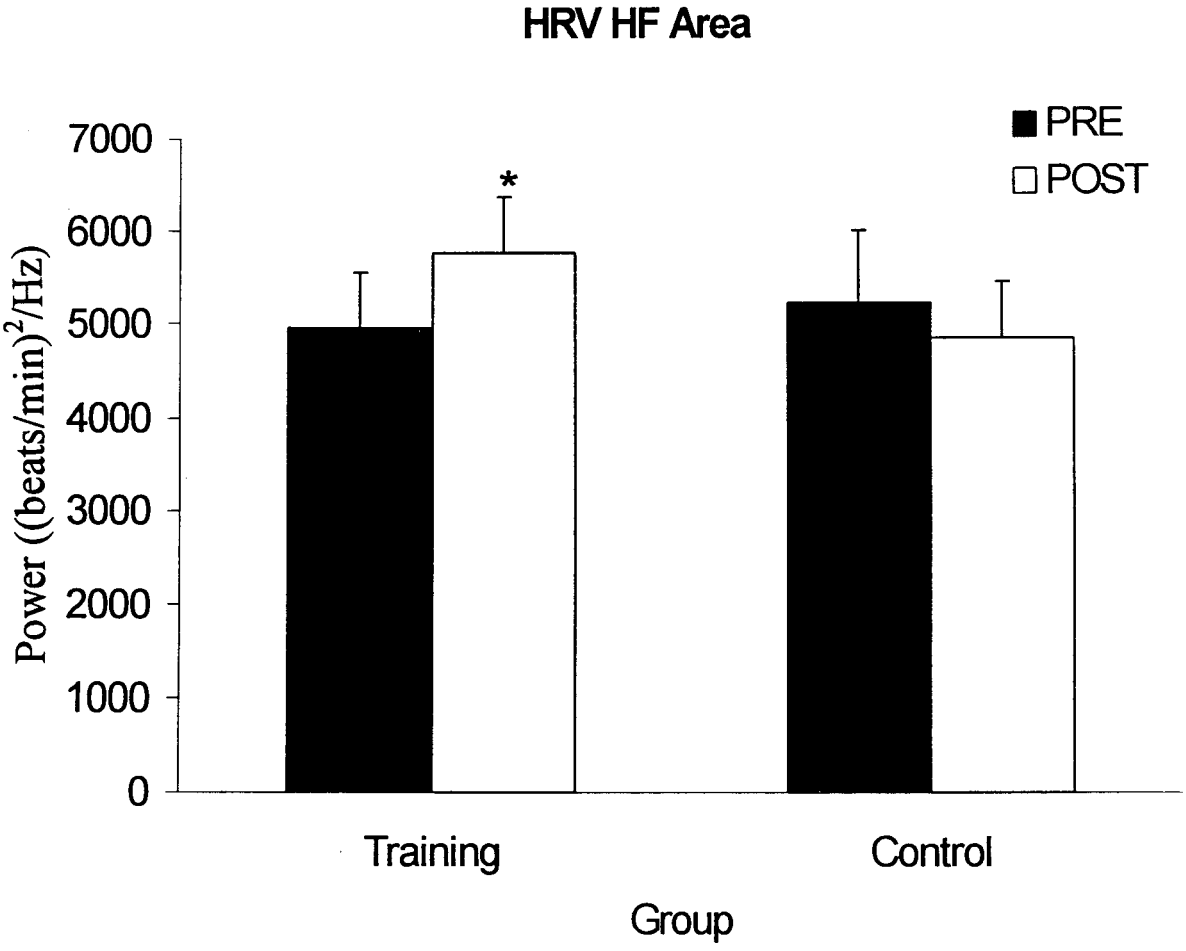

Figure 9. High frequency area of heart rate variability for isometric exercise trained (n=9) group and control (n=6) group. Values are expressed as means (± SE) and represent week 0 and week 10 measurements. The trained group showed a significant ($p<0.05$) increase while the control group showed a change in the opposite direction. Asterisks (*) denote significant differences in HF area pre-training versus post-training.

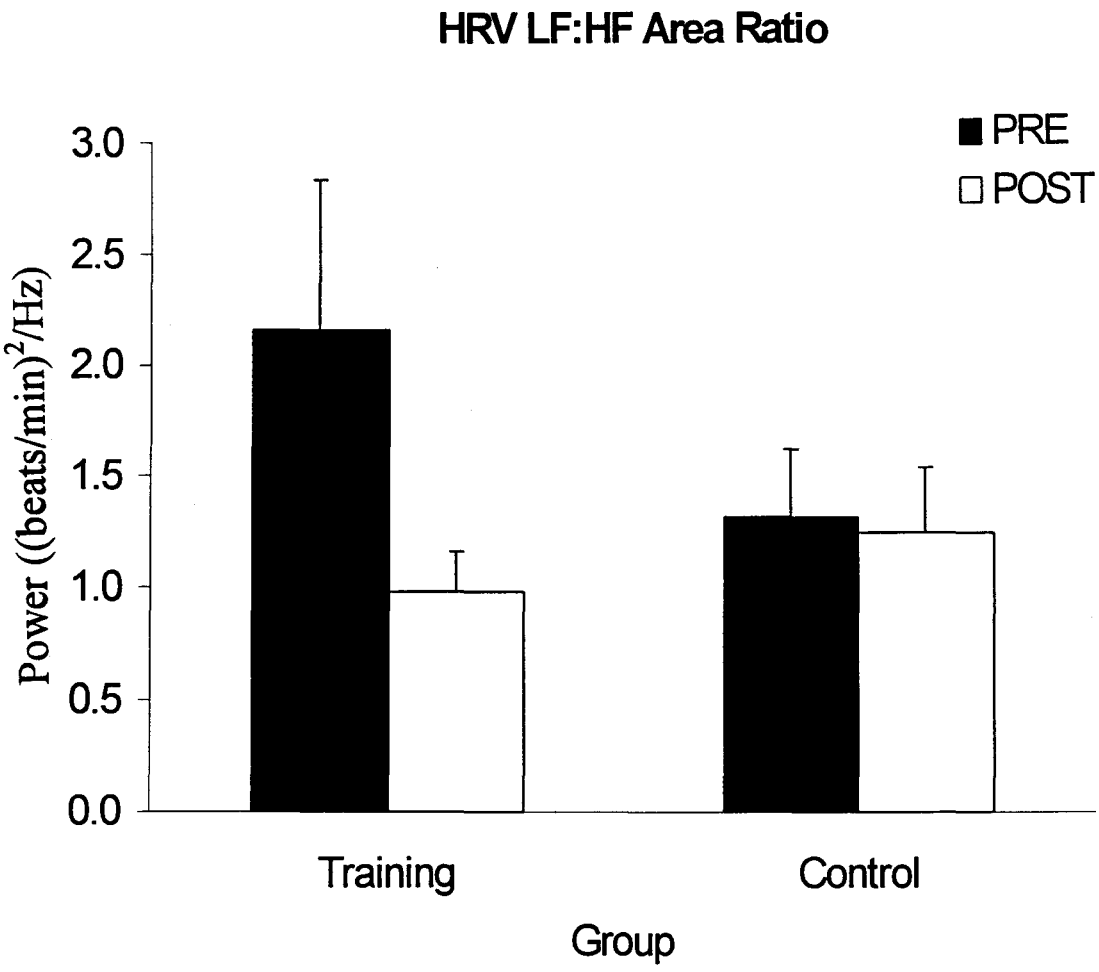

Figure 10. Low frequency/High frequency area ratio of heart rate variability for isometric exercise trained (n=9) group and control (n=6) group. Values are expressed as means (± SE) and represent week 0 and week 10 measurements.

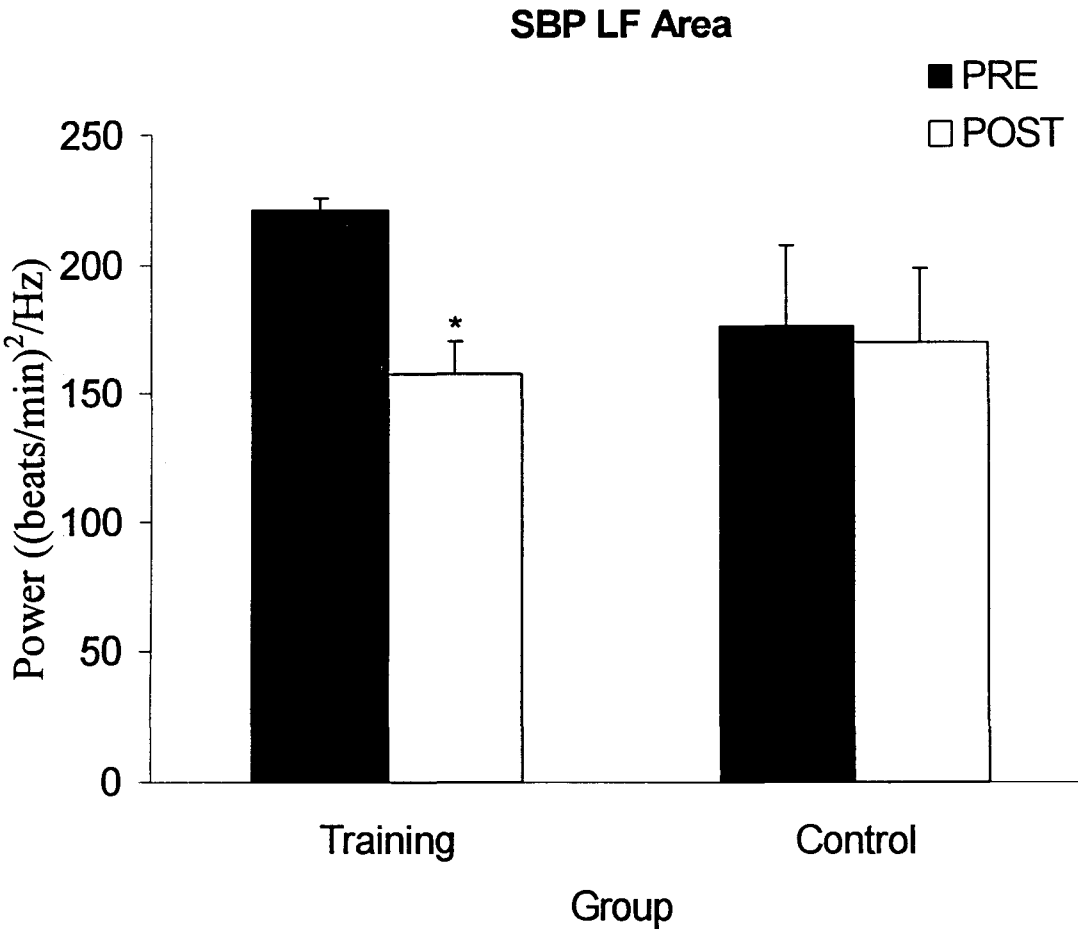

Figure 11. Low frequency area of systolic blood pressure variability for isometric exercise trained (n=9) group and control (n=6) group. Values are expressed as means (± SE) and represent week 0 and week 10 measurements. The trained group showed a significant decrease ($p<0.05$) while the control group did not. Asterisks (*) denote significant differences in LF area pre-training versus post-training.

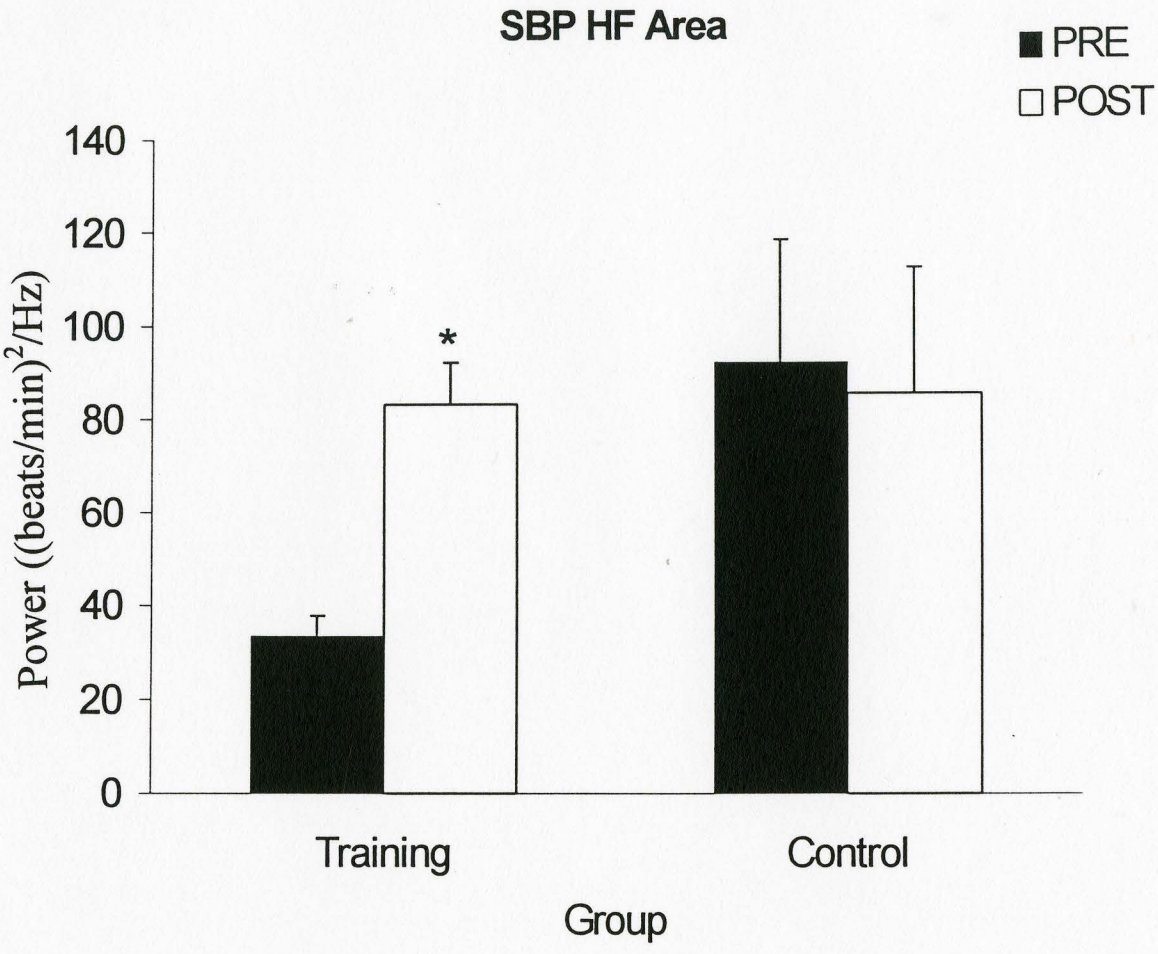

Figure 12. High frequency area of systolic blood pressure variability for isometric exercise trained (n=9) group and control (n=6) group. Values are expressed as means (± SE) and represent week 0 and week 10 measurements. The trained group showed a significant increase ($p<0.05$) while the control group showed a change in the opposite direction. Asterisks (*) denote significant differences in HF area pre-training versus post-training.

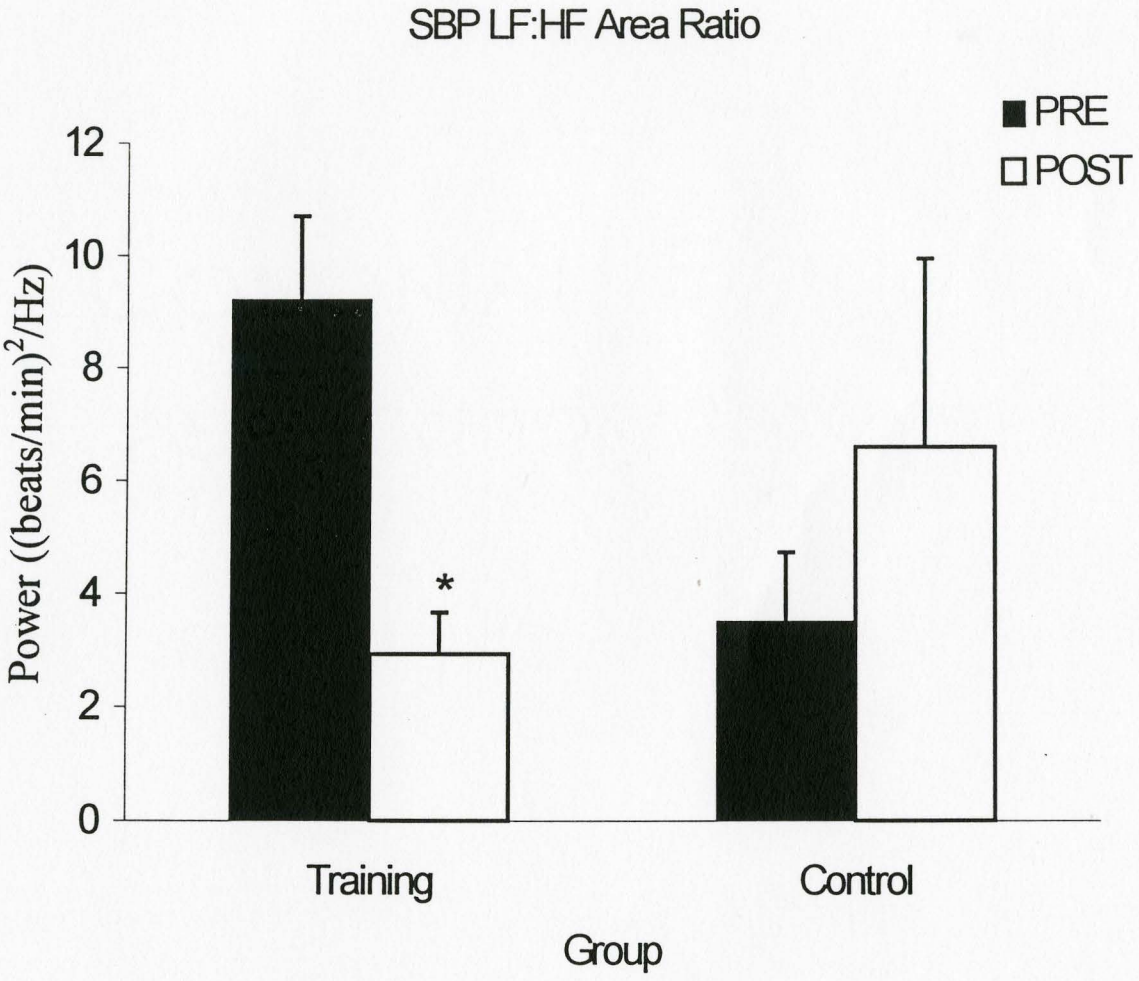

Figure 13. Low frequency/High frequency area ratio of systolic blood pressure variability for isometric exercise trained (n=9) group and control (n=6) group. Values are expressed as means (± SE) and represent week 0 and week 10 measurements. The trained group showed a significant decrease ($p<0.05$) while the control group showed a change in the opposite direction. Asterisks (*) denote significant differences in LF/HF area ratio pre-training versus post-training.

DBP changes are demonstrated in Figures 14, 15 and 16. Analysis of DBP values showed a main effect for TIME for the LF area ($F(1,13)=5.23$; $p<0.04$) and the HF area ($F(1,13)=4.73$; $p<0.05$). The LF:HF area ratio data for DBP showed a downward trend, however the statistical analysis was non-significant. There were no further main effects or interactions for the rest of the DBP data.

3.4 Reproducibility of Power Spectral Heart Rate Variability

A one-way ANOVA was performed on baseline, week 5 and week 10 supine and standing power spectral data of the control group to determine the reproducibility of power spectral indices. During each of the recording sessions, the autospectra of HRV in individual subjects remained constant. Table 2 shows that there was no difference ($p>0.05$) during the supine and standing conditions when repeated over time.

Table 2: Reproducibility of Power Spectral Heart Rate Variability Components

	Test Day 1 (n=6)		**Test Day 2 (n=6)**		**Test Day 3 (n=6)**	
	Supine					
Heart Rate	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
LF Area	5796.6	731.6	5003.42	1160.8	5252.8	1195.2
HF Area	5229.7	1736	4830.4	1573.3	4849.3	1342.9
LF:HF ratio	1.32	0.68	1.32	0.88	1.25	0.64
	Standing					
Heart Rate	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
LF Area	5806.8	1318	6308.58	515.9	6359.44	1175.6
HF Area	3742.65	2111.3	3367.48	1667.9	3472.88	1915.8
LF:HF ratio	1.62	0.64	1.76	0.48	1.83	0.83

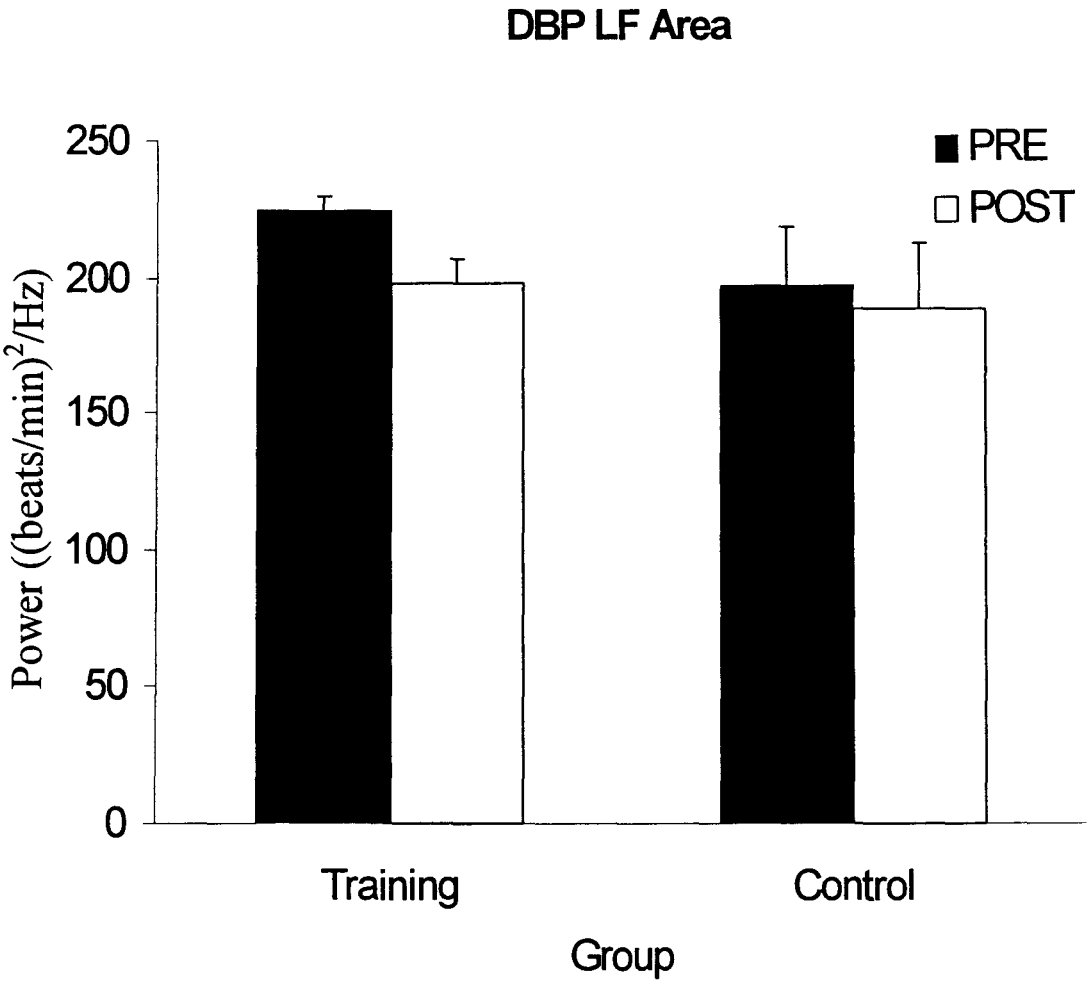

Figure 14. Low frequency area of diastolic blood pressure variability for isometric exercise trained (n=9) group and control (n=6) group. Values are expressed as means (± SE) and represent week 0 and week 10 measurements.

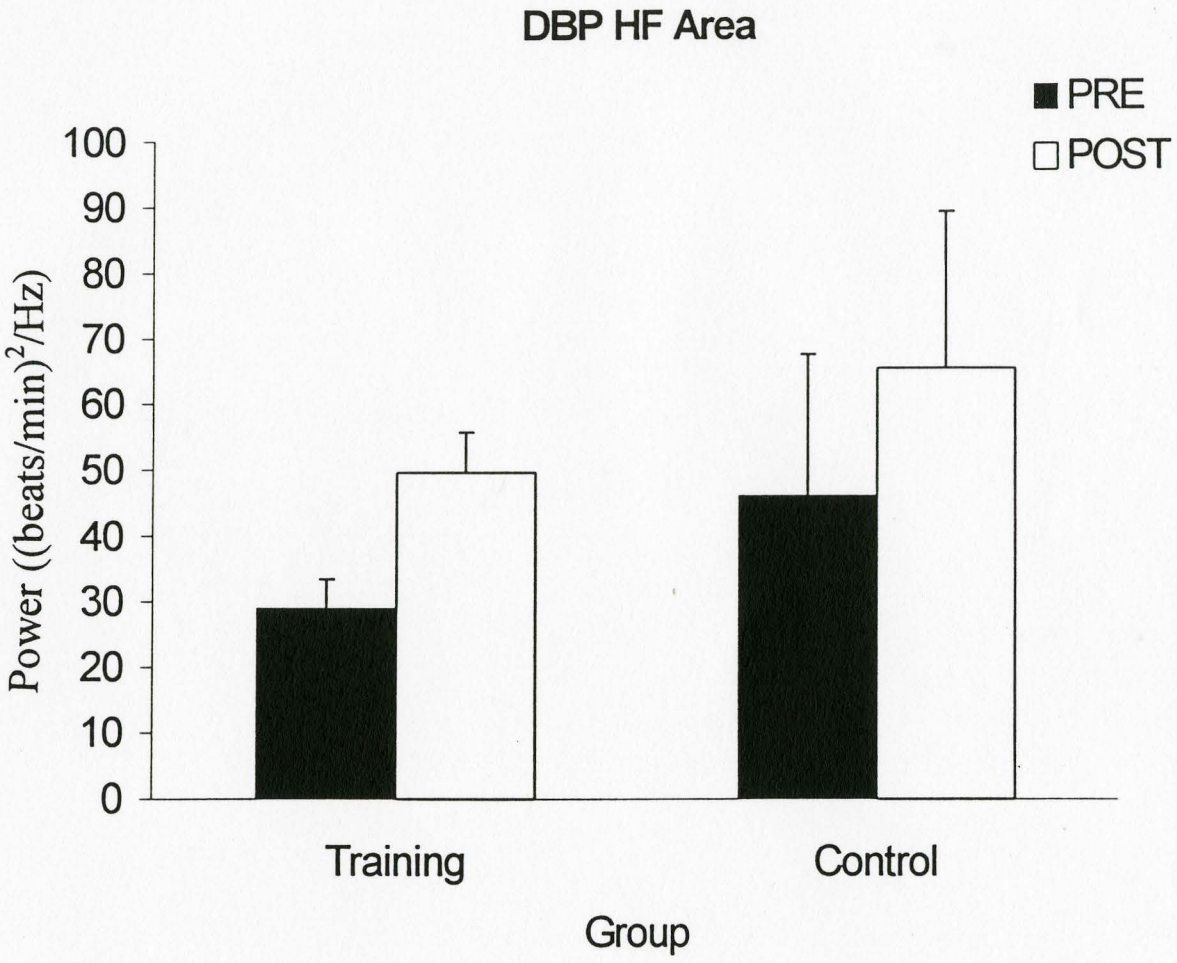

Figure 15. High frequency area of diastolic blood pressure variability for isometric exercise trained (n=9) group and control (n=6) group. Values are expressed as means (± SE) and represent week 0 and week 10 measurements.

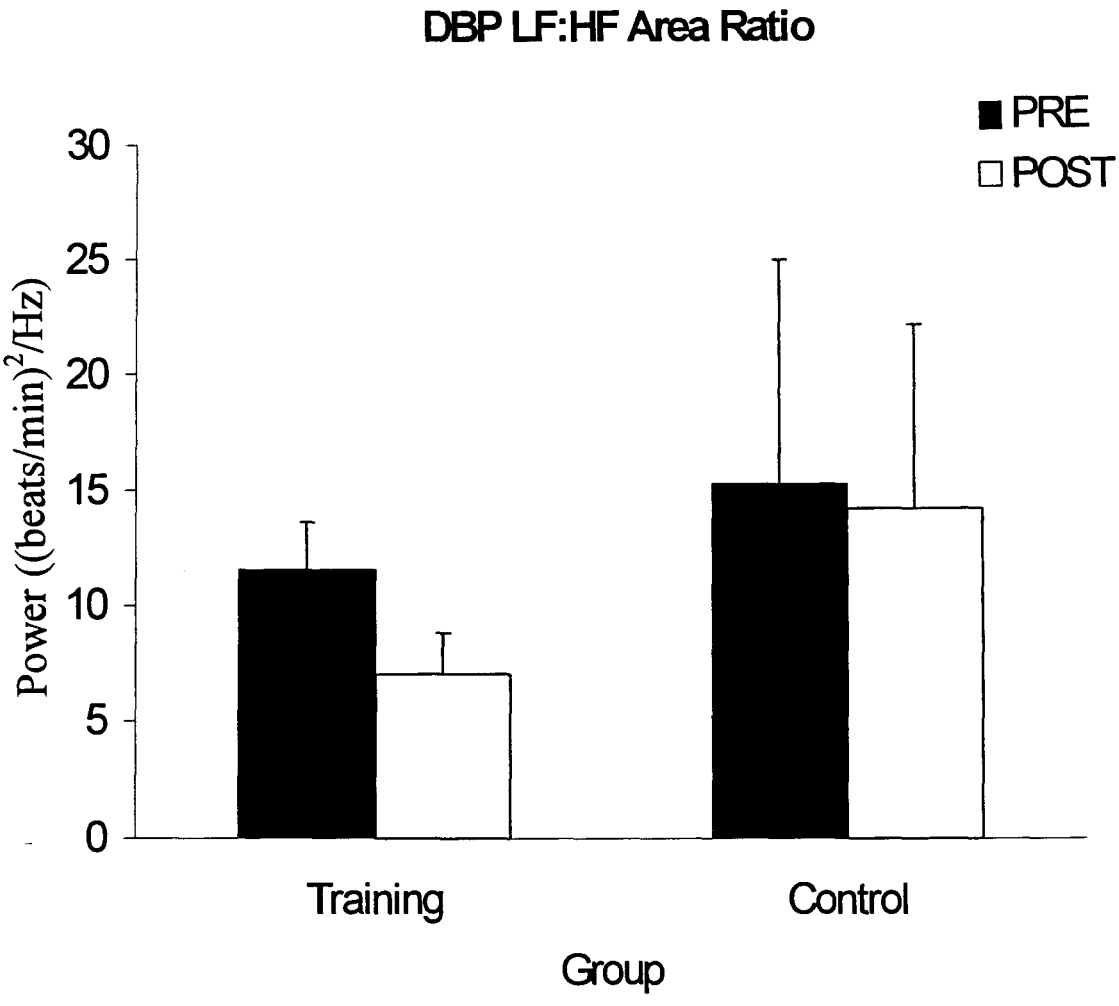

Figure 16. Low frequency/High frequency area ratio of diastolic blood pressure variability for isometric exercise trained (n=9) group and control (n=6) group. Values are expressed as means (± SE) and represent week 0 and week 10 measurements.

3.5 Isometric Maximal Voluntary Contraction (MVC) Strength

Analysis was performed on weekly isometric handgrip MVC values for the right and left hand in the isometric exercise trained group. Before training, the group average for the right hand was a greater MVC than for the left hand but the difference was non-significant. Analysis of MVC strength for the right hand showed an increase in strength that approached significance ($p<0.06$) from 60.3 ± 25.75 pounds for week 1 to 66.0 ± 28.20 pounds for week 10. Alternatively, analysis of MVC strength for the left hand revealed a statistically significant increase from 54.8 ± 23.93 pounds to 63.1 ± 24.18 pounds for week 1 and week 10, respectively ($p<0.000003$). Figure 17 illustrates the change in MVC strength for the right and left hands. Tukey's post hoc procedure for left hand MVC values identified a significant difference at week four, week six, week seven, week eight, week nine and week ten.

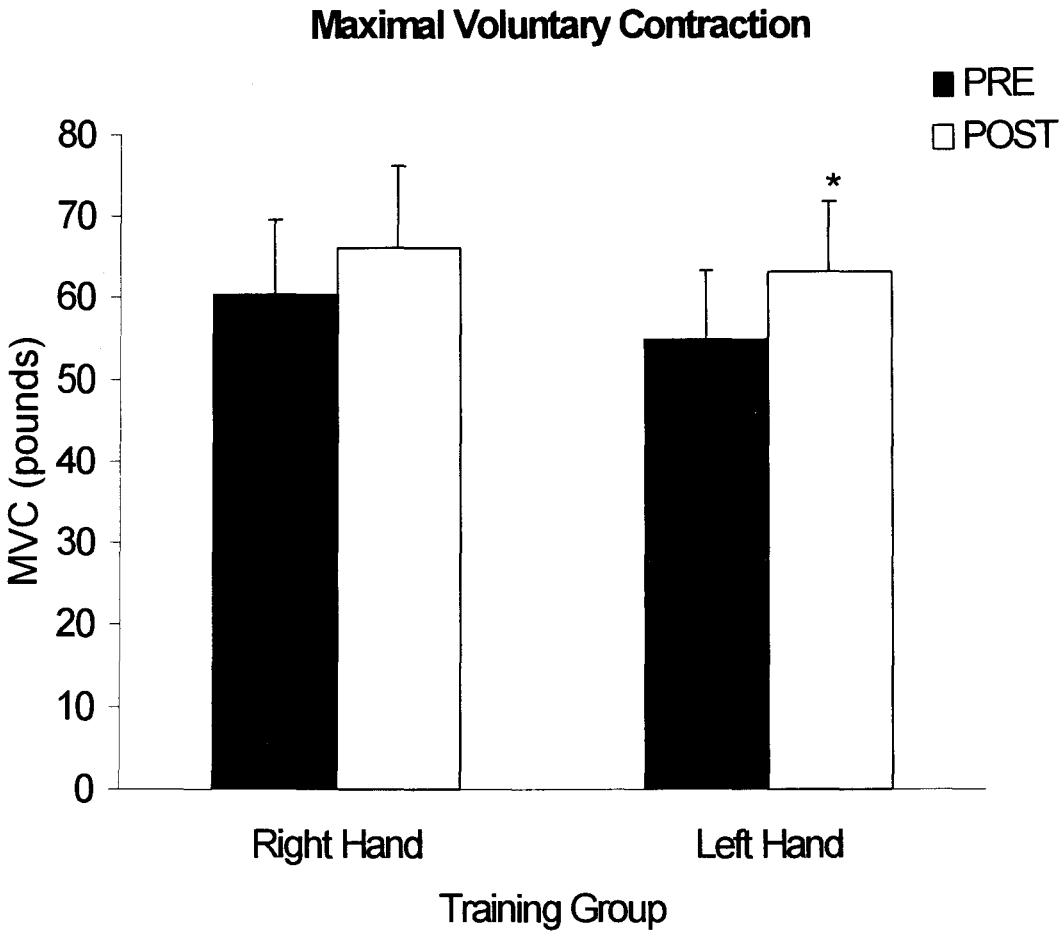

Figure 17. Isometric handgrip MVC strength for the right and left hand in the isometric exercise trained (n=9) group. Values are expressed as means (± SE) and represent week 1 and week 10 values. Both hands showed increases in strength post training. The increase in strength for the left hand was statistically significant ($p>0.000003$). Asterisks (*) denote significant differences.

4.0 DISCUSSION

4.1 Effects of Training on Resting Blood Pressure and Heart Rate

The most significant finding in this study was the attenuated blood pressure response observed after ten weeks of isometric exercise training. A significant reduction in systolic blood pressure and a trend toward a reduction in diastolic blood pressure resulted in a statistically significant decrease in mean arterial pressure ($p<0.025$). Since mean arterial pressure has been defined as the average perfusion pressure that the heart must pump against, the marked attenuation that we observed following training was a significant physiological finding. By attenuating this circulatory component, the left ventricle does not have to contract as forcefully to overcome the resistance of the peripheral vasculature.

The findings in this study confirmed previous reports by Wiley et al. (1992) which suggested that brief repeated submaximal isometric contractions elicited a hypotensive effect in hypertensive subjects. Interestingly, we observed similar reductions in systolic and diastolic blood pressure as those seen by Wiley et al. (1992). Utilizing a similar training intervention, their results for systolic and diastolic pressure showed significant reductions of approximately 13 mm Hg and 15 mm Hg, respectively ($p<0.0001$). In this study, systolic blood pressure was significantly decreased by approximately 19 mm Hg ($p<0.005$) and diastolic blood pressure was lowered by 7 mm Hg. Because both studies measured blood pressure by auscultation we are able to make direct comparisons between our results and those obtained by Wiley et al. (1992). It should be noted that, while the resting DBP downward trend was not significant, the

initial DBP of this group was high-normal. As a group then, these subjects would be defined as Isolated Systolic Hypertensive subjects. Thus, there was an increased likelihood of the exercise stimulus lowering resting SBP then DBP.

The present study and that by Wiley et al. (1992) are novel approaches to a potential non-pharmacological method to treat hypertension. To our knowledge, only two other studies have investigated the effects of isometric training on resting blood pressure in hypertension. These include a study by Kiveloff and Huber (1971) that examined whole body isometric exercise on resting blood pressure and a study by Buck and Donner (1985) which compared occupational isometric stress to the incidence of hypertension. Neither study reported negative physiological effects as a consequence of isometric exercise in their subject populations. However, neither study used a standardized method to quantify the evoked isometric effort, nor did they propose any potential physiological mechanisms contributing to the observed blood pressure reduction.

In the present study, the resting heart rate response to training resulted in a 2 beat/minute reduction in the training group (70 $\pm$ 14.2 beats/min. to 68 $\pm$ 12.1 beats/min.) and a statistically significant 6 beat/minute increase in the control group (70 $\pm$ 8.5 beats/min. to 76 $\pm$ 15.3 beats/min.) ($p<0.04$). Our findings for heart rate are similar to those obtained by Wiley et al. (1992) which showed a 2 beat/minute decrease (78 $\pm$ 7.87 beats/min. to 76 $\pm$ 6.52 beats/min.) and a 5 beat/minute increase (77 $\pm$ 4.57 beats/min. to 82 $\pm$ 8.26 beats/min.) in their training and control groups, respectively. It is worth commenting on the opposite direction of change in heart rate seen between our training

and control group. The decrease (2 beat/min.) in heart rate seen in the training group was non-significant and therefore we can only speculate on mechanisms that might have caused the reduction, which in this case may perhaps be attributed to either enhanced vagal tone or to day to day changes in heart rate variability. The significant increase (6 beat/min.) in resting heart rate for the control group might simply be due to random occurrence.

4.2 Effects of Training on Heart Rate Variability

Power spectral analysis of HRV is thought to represent indices of autonomic modulation. The heart rate signal is subjected to frequency analysis which yields low and high frequency components that represent sympathetic and parasympathetic neural modulatory influences, respectively. In hypertension, HRV power spectra have consistently shown an elevated LF component, while the HF component is blunted or non-existent (Alicandri et al., 1985; Pomeranz et al., 1985; Guzzetti et al., 1988). Guzzetti et al. (1988) reported that, compared with healthy control subjects, the PSA of HRV in subjects with hypertension consistently demonstrated that LF power was significantly increased while HF power was reduced, suggesting an elevated sympathetic modulation in hypertension. In our hypertensive subjects, the PSA of HRV was characteristically similar to that described by Furlan et al. (1987) and Guzzetti et al. (1988). The LF area invariably showed more power than the HF area prior to training.

The results of this study showed that isometric training had the potential to alter sympathovagal balance as measured by power spectra of HRV. Specifically, training led

to changes in the spectral markers of autonomic activity during the resting condition by a simultaneous reduction in sympathetic modulation and an increase in vagal modulation, as the LF component was decreased (6150.34 ± 1002.2 $(beats/min)^2/Hz$ to 5009.62 ± 1506.5 $(beats/min)^2/Hz$) and the HF component was increased (4957.97 ± 1679.7 $(beats/min)^2/Hz$ to 5774.74 ± 1661.51 $(beats/min)^2/Hz$) ($p<0.002$). In addition, there was also a decrease in the LF:HF area ratio following the training intervention (2.16 ± 1.91 $(beats/min)^2/Hz$ to 0.98 ± 0.51 $(beats/min)^2/Hz$).

Some studies have confirmed that endurance trained athletes tend to have a larger vagal component and a smaller sympathetic component at rest compared with their untrained counterparts (Eckblom et al., 1973; Dixon et al., 1992; Tulppo et al., 1998). A change in autonomic regulation after physical training in sedentary individuals has also been demonstrated (Pagani et al., 1988). Pagani et al. (1988) explored the relationship between physical training and HRV in 11 subjects with mild hypertension. Subjects underwent a 6-month training program that consisted of jogging for 20 minutes at least 5 days a week in addition to a daily routine of calithetics. They reported that the training intervention produced a training bradycardia, a decrease in the LF component and an increase in the HF component.

To this author's knowledge there have been no investigations into the effect of isometric training on HRV in hypertension. This study is the first to explore the effects of isometric handgrip training on the autonomic modulation of HRV and BPV and we were able to show an attenuation in sympathetic and an increase in parasympathetic modulation following training. In this study, the effects of training are similar to the

effects of chronic β-adrenergic blockade on hypertension such that heart rate and blood pressure were reduced with a diminution of LF area and an increase in HF area.

The effects of aging on HRV have been confirmed by several investigators (Johnson & Spalding, 1974; O'Brien et al., 1986; Simpson & Wicks, 1988). Generally, it has been found that there is a reduction in HRV with advancing age. However, some studies have documented that HRV can be maintained with a healthy active lifestyle or following a physical conditioning program (Hellman & Stacey, 1976; Hirsch & Bishop, 1981; Harvey, 1996). In the present study, we cannot confirm a reduction in HRV with aging since the training group was only compared to age-matched control subjects and not to control subjects of differing ages.

4.3 Effects of Training on Blood Pressure Variability

Power spectral analysis of blood pressure variability has been measured using a Finapres device and has provided assessment of autonomic modulation of cardiovascular function (Akselrod et al., 1988; Malliani et al., 1991). The LF systolic blood pressure oscillations are thought to correspond to rhythmic changes in vasomotor activity and are mediated by sympathetic control (Pagani et al., 1986). When changes in the LF component or the LF:HF area ratio occur in response to pharmacological or physiological stimuli, they are thought to reflect changes in sympathetic control of blood pressure (Pagani et al., 1992) or sympathovagal balance (Pagani et al., 1986).

The LF and HF autospectrum components of systolic arterial pressure variability are similar to those observed for HRV (Pagani et al., 1986). An increase in arterial

pressure variability has been demonstrated in patients with hypertension and an elevated LF component has been documented during daytime recordings in ambulatory patients (Pagani et al., 1985). The greater LF component in hypertension can be explained by higher sympathetic activity. In this study, we were able to confirm an elevated LF component of arterial pressure with a correspondingly small HF component as is characteristically seen in hypertensive patients. Prior to the exercise intervention, the power of the LF area for the training group was 221.06 ± 12.85 $(beats/min)^2/Hz$ and the power for the HF area was 33.56 ± 12.04 $(beats/min)^2/Hz$. Following training, there was a significant decrease in LF area (157.72 ± 36.4 $(beats/min)^2/Hz$; $p<0.02$) and a significant increase in HF area (83.07 ± 25.21 $(beats/min)^2/Hz$; $p<0.009$). These changes resulted in a significant decrease in the LF:HF area ratio (9.22 ± 4.17 $(beats/min)^2/Hz$ to 2.92 ± 2.08 $(beats/min)^2/Hz$; $p<0.01$). Therefore, the findings of this study suggest that brief, repeated bouts of isometric handgrip exercise lead to decreased sympathetic and enhanced parasympathetic modulation of heart rate and blood pressure after training.

The results for diastolic pressure variability were similar to those observed for systolic pressure variability; following training there was a decrease in LF area, an increase in HF area and a decrease in the LF:HF area ratio, but these changes were not statistically significant.

4.4 Mechanisms Associated with an Attenuated Blood Pressure Response

The present study attempted to identify possible mechanisms associated with the attenuation in blood pressure following isometric training. We measured the PSA of

heart rate and blood pressure variability to non-invasively assess the potential effect that training had on autonomic modulation of heart rate. By using this approach, we were able to obtain an indirect index of sympathetic modulation. Previously, it was suggested that changes in sympathetic neural influences on total vascular resistance might act as sufficient stimulus to produce a decline in blood pressure (Wiley et al., 1992). While it is difficult to identify precise mechanisms responsible for these changes, we cannot eliminate the possibility that the attenuated blood pressure response was in part mediated by alterations in autonomic nervous system activity, as is supported by our findings. Previous investigations have identified alternative mechanisms such as decreased muscle sympathetic nerve activity (Somers et al., 1992; Sinoway et al., 1996), increased muscle blood flow (Sinoway et al., 1987; Joyner, 1991; Dyke, 1998) and baroreceptor resetting (Della Rovere et al., 1986; Pagani et al., 1988).

Following 6 weeks of isometric handgrip training, Sommers et al. (1992) showed attenuation in sympathetic nerve activity in their subjects as measured by microneurography. The investigators proposed that the decrease in sympathetic nerve activity was probably secondary to a reduction in muscle chemoreceptor stimulation. Suprisingly, a reduction in blood pressure did not accompany the decrease in sympathetic nerve activity. The investigators blamed the method of blood pressure measurement for their non-significant finding. Alternatively, they proposed that vasoconstriction in other vascular beds (e.g. mesenteric and renal) might override any blood pressure reductions resulting from the decrease in sympathetic nerve activity in skeletal muscle. Although in the present study we did not directly measure muscle sympathetic nerve activity, we

speculate given that perhaps our subjects also had an attenuated sympathetic nerve activity response to 10 weeks of sustained isometric handgrip training.

In a recent investigation, Sinoway et al. (1996) reported a reduction in muscle sympathetic nerve activity that was accompanied by a decrease in lactate production during forearm exercise after training. They suggested that venous lactate served as a useful marker of metabolic by-product production during exercise. Perhaps the reduction in sympathetic nerve activity resulted from a decrease in metabolite accumulation following training as was suggested by Mostoufi-Moab et al. (1998). If this is the case, endurance forearm training might have the potential to decrease anaerobic metabolism and increase aerobic metabolism during exercise (Sommers et al., 1992). Other investigators have suggested that the measurement of muscle sympathetic nerve activity can be used as an indirect index of chemosensitive muscle afferent activation (Victor et al., 1988; Pryor et al., 1990; Joyner & Weiling, 1993). This is because there is little or no increase in sympathetic nerve activation during handgrip work until the chemoreceptors are stimulated by a decrease in muscle pH and other metabolites.

Another physiological adaptation documented following training is an increase in blood flow to the exercising muscle. It is uncertain as to whether the increased flow is the result of reduced sympathetic vasoconstrictor influences (Clausen et al., 1973) and/or the result of increased intrinsic vasodilatory capacity (Sinoway et al., 1987; Ferguson & Brown, 1997). Sinoway et al. (1987) reported that after 4 weeks of handgrip exercise, a localized training induced increase in forearm blood flow occurred that was associated with an increase in vascular vasodilatory capacity. The increase in blood flow resulted

from a decrease in minimal peripheral resistance. This adaptation could possibly explain the attenuated blood pressure response seen in our investigation.

Many investigators have associated hypertension and aging independently to a diminished baroreceptor reflex sensitivity (Bristow et al., 1969; Gribbon et al., 1971; Mancia et al., 1980). The decrease in baroreceptor sensitivity has been documented to result from reduced compliance of the arterial vasculature, whereby there is less stretch of the receptor per unit rise in blood pressure (Bristow et al., 1969). Also, it has been hypothesized that in hypertension, the baroreceptors are reset to meet the changing demands of a higher pressure level in addition to maintaining a decreased sensitivity. The issue that arises from these studies is whether a diminution in the integrity of the baroreceptors can be reversed. Few studies have investigated the possibility that exercise training can positively alter baroreceptor activity. An increase in the gain of the baroreflex has been reported in conscious dogs (Billman et al., 1984) and patients with previous myocardial infarction (Della Rovere et al., 1986) after training. Pagani et al. (1988) investigated the effects of physical training on the gain of baroreceptor reflex sensitivity in 11 subjects with hypertension. They reported that following training there was a decrease in heart rate, a decrease in blood pressure and a corresponding increase in baroreceptor sensitivity. They measured baroreceptor sensitivity with phenylephrine injection where the slope of the regression line relating the pulse interval per unit rise in blood pressure is taken as an index of baroreceptor reflex sensitivity. Their results showed a change in the slope of the regression line from 14.7 ± 2.5 msec/mm Hg in the untrained state to 19.5 ± 2.7 msec/mm Hg in the trained state. These findings provided

evidence to suggest that exercise training could enhance sensitivity of the baroreceptors in hypertensive subjects. The exact mechanism responsible for altering baroreceptor sensitivity is not known. However, speculation has centered around the possibility that repeated exposure to the pressor response during exercise might stimulate the baroreceptors and therefore lead to increased sensitivity or a resetting to a new baselin after training.

We did not measure baroreceptor sensitivity in the present study. However the decrease in resting blood pressure and heart rate seen in our study is comparable to the reductions reported by Pagani et al. (1988). Taken together, we can speculate that continued exposure to the pressor response during our isometric training intervention led to an increase in the baroreceptor reflex sensitivity of our hypertensive subjects. The resulting interaction of the baroreceptors with the medulla would then increase the sympathetic inhibitory signals and inhibit the sympathetic excitatory signals to the heart, thus explaining the changes in heart rate and blood pressure observed in our study.

Because we did not directly measure muscle sympathetic nerve activity, muscle blood flow or baroreceptor sensitivity, no firm conclusions can be drawn about whether these mechanisms contributed to the blood pressure reduction reported in our study. However, it is possible that any or all of these mechanisms could have played a role in the attenuated blood pressure response. To determine the extent to which these mechanisms could have influenced our results would require further investigation.

4.5 Reproducibility of Power Spectral Heart Rate Variability Components

Power spectral analysis of HRV is being increasingly used to provide an index of autonomic activity in healthy (Mukai et al., 1995) and diseased states (Guzetti et al., 1995). In order for this method to be accepted as a diagnostic technique, its repeatability and reproducibility must be considered. Kamath et al. (1988) have outlined 3 crucial criteria that must be met if PSA of HRV is to be used clinically to assess autonomic nervous system function. The criteria are as follows: 1) both short-term acute and long-term chronic recordings should be reproducible during repeated trials; 2) the response to physiological stress should alter sympathovagal balance in a predictable and repeatable manner; and 3) the PSA of HRV rhythms should correlate with sympathetic and parasympathetic components of the autonomic nervous system.

Pagani et al. (1986) showed the reproducibility of short-term variability as assessed by tilt and long-term variability during 3 recording sessions that were separated by an average of 138 days and 127 days, respectively. During each trial, the R-R variability, indicated by the LF and HF power, remained constant when repeated over time in the resting and tilt conditions with an interval of up to a year ($p>0.05$). In a similar investigation, Cloarec-Blanchard et al. (1997) measured the repeatability of spectral components of short-term HRV during sympathetic activation in 23 healthy young men. Following either nitroglycerin infusion ($n=10$) or 60 degree head-up tilt ($n=13$), there was a predictable increase in the LF component and the LF:HF area ratio of HRV, indicating a shift in the sympathovagal balance toward sympathetic predominance. The investigators reported that the changes in the spectral components of HRV for the

control and tilt conditions were reproducible on a subsequent study day, indicating that the repeatability was stable over time.

In the present study, we were able to successfully meet the PSA of HRV criteria outlined by Kamath et al. (1988). Based on the analysis performed on our control subjects, we were able to confirm that the power spectral components of R-R variability remained constant when repeated over time. Our study provided reproducible results during short-term acute and long-term chronic recordings in the supine and standing conditions during 3 separate recording sessions ($p>0.05$). In addition, our results showed a shift in the sympathovagal balance of HRV that was predictable and repeatable. This shift was indicated by a change in the LF and HF components from the supine to the standing condition. There was LF predominance and a predictably larger LF:HF area ratio upon standing that occurred during all three recordings. Furthermore, the power spectrum for individual subjects showed rhythms that consistently corresponded with specific branches of the autonomic nervous system. Having met the 3 previously outlined conditions, we believe that the repeatability and reproducibility of our HRV spectral indexes was satisfactory.

4.6 Effects of Training on Isometric Handgrip MVC Strength

Exercise studies that have assessed conditioning of various muscle groups have documented increases in strength following a specified training period (Wilmore et al., 1978; Harris et al., 1987; Dupler & Cortes, 1993; McCartney et al., 1996). Endurance training of smaller muscle groups such as the muscles of the hand and forearm has been

shown to result in either an increase in strength (Sinoway et al., 1987) or no change (Somers et al., 1992; Sinoway et al., 1996) after training. Somers et al. (1992) reported that forearm strength before endurance handgrip training was greater in the right arm than the left arm ($p<0.05$), but following training there was no change in MVC strength for either the endurance trained right arm or the sham trained left arm. Similarly, Sinoway et al. (1996) reported no change in MVC strength of the trained arm following 4 weeks of unilateral forearm conditioning. In addition, they reported a 4% decrease in MVC strength in the untrained arm ($p<0.05$) post training. Alternatively, in a previous study Sinoway et al. (1987) reported an increase in maximal forearm tension in both arms following a 30 day forearm work protocol, but neither increase reached statistical significance.

Unlike the rhythmic handgrip contraction protocols used in the aforementioned studies, we utilized a sustained isometric handgrip protocol that included four 2-minute contractions using alternate hands. Throughout the 10 week duration of the training intervention, subjects consistently demonstrated weekly improvements in forearm MVC strength. Therefore, we continued to alter the IHG training workload to keep the required effort of 30% MVC constant. Had we not altered the workload each training session by having subjects produce new MVC values, the absolute effort of the contraction would have been less than 30% MVC. Thus, by monitoring weekly MVC changes, we were able to keep the relative effort of the contraction consistent over the 10 week period. Following training we observed a 5.7 ± 2.45 pound increase in MVC strength that approached statistical significance ($p<0.06$) for the right hand. In addition, we observed a

statistically significant 8.3 ± 0.25 pound increase in MVC strength for the left hand ($p<0.000003$). Unfortunately we did not measure forearm girth prior to training and therefore we cannot determine if the improvements that we observed in strength were the result of an increase in muscle cross-sectional area. Previous resistance training studies have shown that improvements in muscle cross-sectional area corresponded to significant improvements in strength after training (Sale et al., 1988; Sale et al., 1994). Another potential mechanism that could be associated with the increase in MVC strength is an improvement in nervous system activation. A possible neural adaptation includes an increased motor unit recruitment (Sale et al., 1994). Alternatively, it is possible that subjects simply became more comfortable with the apparatus and more coordinated in their effort and thus, they were able to produce maximal contractions more effectively.

4.7 *Confounding Factors*

Due to the nature of this research, there are several potential confounding variables that could have influenced our results. Our primary dependent variables were blood pressure and heart rate, both of which are highly variable (Pickering et al., 1997; Watson et al., 1980) over a 24 hour period. We attempted to minimize the effects of exogenous stimuli by controlling the environmental conditions, by utilizing the same equipment each measurement day and by using an age-matched control group. However, we cannot dismiss the possibility that lifestyle or behavioural factors could have influenced individual blood pressure responses.

Another potential confounding factor was the power of our investigation (n=17). Because of the duration, the location and the time commitment of the study, we were only able to recruit 9 participants for the training group and 8 participants for the control group. Perhaps if the sample population were larger we could have attained statistically significant values for some of our HRV data. Nevertheless, we were able to produce significant reductions in systolic pressure, mean arterial pressure and indices of blood pressure variability. Also the findings we reported for diastolic blood pressure held clinical significance in that the reductions we observed were as low as those reported for other non-pharmacological methods of blood pressure reduction (Seals et al., 1984).

Our method of blood pressure measurement can also be scrutinized. We measured blood pressure using auscultation with a mercury sphygamomanometer and stethoscope. Auscultation has been recommended as a useful method for measuring blood pressure (Kirkendall et al., 1980), however, it has been criticized for experimenter bias in the values obtained. To minimize this effect, we measured resting blood pressure three times each session and averaged the values to obtain a mean pressure. We could have chosen a more precise method of blood pressure measurement such as intra-arterial catheter insertion however the aims of the study did not justify this method. We are confident that the values obtained were accurate since the auscultatory method has been compared with other methods of blood pressure measurement and has been shown to provide similar values.

5.0 SUMMARY AND FUTURE DIRECTION

Previous studies have shown that aerobic and resistance exercise have positive influences on cardiovascular responses to training in healthy subjects and in subjects with hypertension. There have been consistent reports that resting blood pressure is attenuated and indices of HRV are altered following training. Power spectral analysis of HRV has been used as a non-invasive tool to assess neurocardiac function. Two distinct spectral peaks have been identified and are thought to correspond to modulation of the sympathetic and parasympathetic nervous systems. A shift in the power spectra of HRV toward a larger HF component, corresponding to vagal modulation and a smaller LF component, corresponding to sympathetic modulation has been observed in individuals examined in the untrained versus the trained state.

This study was the first to investigate the effects of isometric handgrip training on resting blood pressure, heart rate and blood pressure variability in a population of older adults with hypertension. We were encouraged by our positive findings and we propose that future research be directed toward investigating alternative mechanisms that might contribute to a reduction in blood pressure. Possible mechanisms include muscle sympathetic nerve activity, changes in forearm muscle blood flow, changes in cardiac output or total peripheral resistance or possible resetting of the baroreceptors.

The present study explored the relationship between isometric training and subsequent modulation of specific branches of the autonomic nervous system. We showed that training attenuated the resting blood pressure response and that a corresponding change in sympathovagal balance occurred following the training

intervention. A shift in the power spectra of HRV and BPV from LF predominance prior to training to HF predominance after training was demonstrated in our hypertensive subjects during supine rest.

We conclude that isometric handgrip training at a modest intensity could be a useful adjunct to pharmacological treatment or could exert enough impact on blood pressure in selective individuals to substantiate its use in isolation as a non-pharmacological therapy to treat hypertension. Multi-center trials should be conducted to determine the impact of this new treatment. It could ease the financial burden associated with pharmacological management.

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SECTION 6.0:

APPENDICES

APPENDIX A:

CONSENT FORM

CONSENT FORM

The effects of ten weeks of isometric handgrip training on resting blood pressure, heart rate variability and blood pressure variability

INVESTIGATORS	ADDRESSES	TELEPHONE
Dr. N. McCartney	Dept. of Kinesiology	(905) 525-9140 x24469
Ms. A. Taylor	Dept. of Kinesiology	(905) 525-9140 x24625 or (905) 567-3694

Purpose

Recent evidence has suggested that short duration, isometric handgrip training lowers resting blood pressure. The purpose of the present study is to a) validate these preliminary findings and b) to determine some potential mechanisms.

Procedure:

Basal Measurements

Initial testing measurements will require you to undergo baseline resting ECG (heart rate), respiration (breathing) and blood pressure readings for a duration of 30 minutes (15 min. lying down, 5 min. sitting and 10 min. standing) using 6 recording chest electrodes and an automated finger pressure monitor (Finapres). In addition, auscultatory (cuff and stethoscope) measurement of blood pressure will also be taken.

Allocation To Group

All subjects will undergo initial basal measurements after which subjects will be randomly assigned to an experimental group and a control group. Experimental group subjects will follow the procedures outlined below. The control group subjects will be required to report to the laboratory one day a week for a weekly blood pressure recording using the auscultatory technique. In addition, control subjects will be asked to report to the lab at week five and week ten of training for mid- and post-training basal measurements.

Training Sessions

After the initial session, experimental group subjects will be asked to report to the laboratory 3 times per week for a ten week period. You will be requested to provide 1 maximal voluntary contraction (MVC) for each hand (left and right) using a

computerized handgrip dynamometer. 30% of the average maximal contraction will be calculated for a target contraction load. During these sessions, you will perform four, 2 minute isometric handgrip contractions with 1 minute of rest between contractions. The contractions will be performed at the calculated 30% of your maximum using alternate hands. In addition, resting blood pressure using the auscultatory technique will be taken on the third training day of each week. And finally, subjects will be expected to undergo mid- and post-training basal recordings at week five and week ten of training.

Post Test Measurements

Resting ECG, respiration and blood pressure measurements will be recorded as above.

Potential Risks:
Handgrip exercise may cause slight muscle strains. A supervised, adequate warm-up should alleviate this problem. There are no other foreseeable risks associated with this study.

Withdrawal:
You will be free to withdraw at any point during the study without repercussion. If you choose to withdraw, you will be permitted to view your collected data to date, after which point, that data will be destroyed.

Confidentiality:
The data will be stored inside a locked filing cabinet within a locked office located in the Human Performance Laboratory. Only the listed investigators will have access to this data.
Collected data will be used in the preparation of scientific manuscripts. You will in no way be identified in resulting publications or presentations

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Having read the above information, I consent to participate in all aspects of the study. I

am aware that I am able to withdrawal at any time without repercussion.

Date	Signature
Date	Witness

APPENDIX B:

RAW DATA

Systolic Blood Pressure Data

Training Group

Subject	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10
1	157	157	150	154	143	144	151	141	149	149	143
2	162	162	142	142	155	160	142	142	140	142	135
3	171	169	159	164	155	140	162	143	156	149	139
4	145	142	142	137	136	128	127	128	130	133	126
5	164	177	170	166	162	173	152	160	161	152	154
6	144	142	153	138	142	138	137	134	135	140	136
7	162	138	135	134	130	132	133	133	158	134	131
8	155	156	152	138	142	144	152	136	156	141	137
9	147	143	149	142	142	132	134	140	145	147	136

Control Group

Subject	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10
1	156	149	146	137	141	131	141	145	149	149	140
2	142	155	151	153	150	157	165	163	141	148	144
3	160	152	147	148	165	156	153	151	155	155	150
4	152	145	156	156	157	144	155	164	142	143	127
5	164	159	175	173	155	170	172	167	150	180	167
6	152	147	147	145	158	140	144	143	143	151	141
7	142	153	140	150	157	144	144	147	144	131	135
8	150	138	144	160	160	141	147	157	158	155	147

Diastolic Blood Pressure Data

Training Group

Subject	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10
1	94	93	86	88	89	89	91	87	91	90	90
2	79	79	72	69	72	69	75	71	65	68	58
3	91	95	74	87	76	75	83	70	76	72	71
4	81	72	70	66	67	70	71	71	74	74	71
5	86	89	90	82	79	90	81	87	87	85	83
6	75	75	82	85	76	69	70	83	84	80	80
7	85	82	82	85	86	86	78	80	86	79	77
8	87	80	83	84	88	92	92	76	88	87	84
9	63	66	64	72	75	63	61	64	64	69	60

Control Group

Subject	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10
1	100	80	82	88	84	84	80	87	91	91	88
2	91	96	93	97	90	99	97	98	84	93	97
3	95	100	90	93	101	94	89	100	96	91	86
4	77	79	83	82	76	79	83	90	81	79	76
5	98	94	93	90	83	90	90	86	82	100	92
6	79	80	89	83	95	85	80	82	86	91	79
7	70	75	72	73	70	77	70	73	79	79	67
8	87	92	93	98	91	88	89	96	93	98	87

Mean Arterial Blood Pressure Data

Training Group

Subject	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10
1	115	114	107	110	107	107	111	105	110	110	108
2	107	107	95	93	100	99	97	95	90	93	84
3	118	120	102	113	102	97	109	94	103	98	94
4	102	95	94	90	90	89	90	90	93	94	89
5	112	118	117	110	107	118	105	111	112	107	107
6	98	97	106	103	98	92	92	100	101	100	99
7	111	101	100	101	101	101	96	98	110	97	95
8	110	105	106	102	106	109	112	96	111	105	102
9	91	92	92	95	97	86	85	89	91	95	85

Control Group

Subject	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10
1	119	103	103	104	103	100	100	106	110	110	105
2	108	116	112	116	110	118	120	120	103	111	113
3	117	117	109	111	122	115	110	117	116	112	107
4	102	101	107	107	103	101	107	115	101	100	93
5	120	116	120	118	107	117	117	113	105	127	117
6	103	102	108	104	116	103	101	102	105	111	100
7	94	101	95	99	99	99	95	98	101	96	90
8	108	107	110	119	114	106	108	116	115	117	107

Baseline Supine Heart Rate & Blood Pressure Variability Data

Subject	Group	AR Method			SBP			DBP			RESP		
		LF area	HF area	LF:HF	LF area	HF area	LF:HF	LF area	HF area	LF:HF	LF area	HF area	LF:HF
1	1	6951.12	3230.46	2.24	230.55	24.86	10.48	241.84	13.79	19.98	76.97	169.71	0.54
2	1	5181.90	7685.22	0.70	230.26	25.42	14.12	231.29	24.18	15.85	24.51	224.12	0.12
3	1	6629.82	3448.41	1.99	211.22	44.24	5.59	231.94	23.36	11.29	117.10	134.05	0.92
4	1	7889.57	3527.24	2.24	211.51	43.57	5.19	221.73	32.82	8.18	25.11	205.81	0.13
5	1	5836.04	7268.51	0.81	228.98	25.97	12.69	213.65	40.45	6.28	44.45	198.04	0.23
6	1	5321.31	5855.46	0.94	237.84	17.41	15.02	241.09	14.09	19.67	31.03	218.40	0.16
7	1	4768.30	5354.06	0.90	228.45	26.19	10.03	204.57	48.92	4.26	8.71	236.02	0.04
8	1	5944.52	4390.20	1.36	199.50	52.60	4.20	208.29	40.12	7.66	38.56	206.86	0.19
9	1	6830.54	3862.18	1.94	211.25	41.79	5.63	230.98	22.57	10.69	43.89	200.85	0.24
10	2	4585.39	6495.09	0.72	48.34	206.27	0.24	125.21	129.01	1.12	44.99	197.62	0.24
11	2	6341.36	5756.11	1.10	204.97	50.20	8.11	235.58	19.17	21.60	134.50	114.29	1.61
12	2												
13	2												
14	2	6159.40	5913.05	1.05	196.45	58.18	4.36	191.12	62.70	3.83	45.46	191.19	0.24
15	2	5332.75	6937.29	0.81	460.21	91.22	1.82	162.08	88.22	1.88	37.39	201.04	0.19
16	2	6546.31	3866.09	1.71	194.12	59.55	3.39	219.59	35.04	6.53	71.55	174.86	0.42
17	2	5814.56	2410.65	2.51	252.70	87.04	3.17	250.48	5.20	56.61	67.96	179.27	0.43

Week # 5 Supine Heart Rate & Blood Pressure Variability

Subject	Group	AR Method			SBP			DBP			RESP		
		LF area	HF area	LF:HF	LF area	HF area	LF:HF	LF area	HF area	LF:HF	LF area	HF area	LF:HF
1	1	7286.46	4122.80	1.77	229.47	26.19	8.95	159.01	86.28	2.61	9.29	241.54	0.04
2	1	4426.98	10872.00	0.42	229.28	26.26	9.41	200.42	52.86	4.58	42.15	207.09	0.24
3	1	5141.68	5299.65	0.95	172.95	82.48	2.63	209.04	46.26	5.20	47.73	194.83	0.25
4	1	5983.29	4068.89	1.48	190.30	63.51	3.75	197.95	53.96	4.80	18.28	224.73	0.08
5	1	4941.57	6471.05	0.77	192.14	60.61	3.77	226.23	28.34	10.54	56.71	189.13	0.37
6	1	5684.85	7141.25	0.81	183.90	66.91	3.01	217.98	34.02	7.04	8.88	239.02	0.04
7	1	5203.49	5322.42	1.01	192.89	53.58	4.27	196.82	54.32	3.96	98.96	139.56	1.15
8	1	4524.15	4864.75	1.08	144.89	103.71	1.56	176.75	75.39	2.44	135.11	110.94	1.31
9	1	6098.81	3918.29	1.64	202.37	50.56	8.15	237.02	18.01	23.05	65.93	180.12	0.45
10	2	4098.08	5778.97	0.71	65.75	187.61	0.38	110.35	143.45	0.83	93.52	156.58	0.71
11	2	5883.79	3485.89	1.82	185.04	63.51	7.56	223.48	27.73	12.39	106.96	141.34	0.77
12	2												
13	2												
14	2	4534.80	6022.50	0.76	93.20	159.82	0.59	111.66	141.51	0.81	16.69	212.61	0.08
15	2	3405.28	6507.93	0.53	145.99	106.14	1.39	169.93	80.84	2.51	118.73	128.30	1.11
16	2	5748.39	4682.96	1.26	193.50	59.32	4.27	226.64	25.94	14.41	77.67	163.44	0.53
17	2	6350.20	2503.96	2.84	251.73	64.25	4.11	251.86	3.90	70.79	116.08	121.86	2.09

Week # 10 Supine Heart Rate & Blood Pressure Variability

Subject	Group	AR Method			SBP			DBP			RESP		
		LF area	HF area	LF:HF	LF area	HF area	LF:HF	LF area	HF area	LF:HF	LF area	HF area	LF:HF
1	1	1831.90	4486.92	0.40	87.04	66.32	1.31	148.66	53.45	3.14	29.20	216.82	0.14
2	1	3857.59	8392.80	0.48	457.27	93.05	1.77	207.09	45.72	8.11	125.81	125.39	1.24
3	1	5550.53	4958.59	1.13	163.60	90.91	2.61	195.56	58.57	5.34	97.64	147.52	0.70
4	1	6588.16	3596.15	1.98	126.06	127.24	1.08	181.82	69.16	3.57	49.53	173.13	0.30
5	1	4667.91	8230.65	0.59	190.73	63.51	3.69	196.48	58.87	3.37	68.17	181.77	0.40
6	1	5778.08	6503.13	0.88	450.66	98.67	1.56	220.09	33.16	7.09	19.47	230.66	0.09
7	1	4738.24	5849.76	0.88	175.31	72.48	5.15	183.04	68.04	7.39	67.52	133.52	0.51
8	1	5325.75	5393.91	1.01	155.29	94.95	1.90	210.61	43.38	5.62	81.21	168.08	0.55
9	1	6758.45	4560.79	1.51	213.48	40.47	7.24	240.03	14.75	19.59	101.78	137.95	0.76
10	2	4526.90	6417.16	0.72	72.68	180.00	0.51	138.50	114.51	1.83	26.76	208.04	0.13
11	2	5289.07	5162.00	1.08	179.84	73.38	2.87	216.47	37.62	6.18	147.72	103.34	1.62
12	2												
13	2												
14	2	3705.30	4752.90	0.79	126.29	125.94	1.75	130.72	122.85	2.07	75.76	159.80	0.81
15	2	4700.50	6141.58	0.78	166.06	82.83	2.05	152.83	100.07	1.54	83.48	159.78	0.55
16	2	6536.65	3174.40	2.08	234.98	19.57	15.87	246.36	8.29	40.96	79.55	146.52	0.62
17	2	6758.38	3445.66	2.05	237.61	30.69	16.44	246.20	8.97	32.40	91.77	151.37	0.64

Baseline Standing Heart Rate & Blood Pressure Variability Data

Subject	Group	AR Method			SBP			DBP			RESP		
		LF area	HF area	LF:HF	LF area	HF area	LF:HF	LF area	HF area	LF:HF	LF area	HF area	LF:HF
1	1	7230.65	2177.32	3.34	233.84	21.55	12.19	241.45	13.55	20.72	137.84	107.89	1.45
2	1	6226.07	5910.45	1.07	243.73	12.03	23.62	274.08	8.51	31.45	147.22	102.60	1.49
3	1	5141.68	5299.65	0.95	172.95	82.48	2.33	209.04	46.26	5.20	47.73	194.83	0.25
4	1	6585.63	2995.91	2.20	214.48	40.04	5.77	235.16	19.83	12.96	96.60	146.35	0.67
5	1	5967.56	5174.68	1.18	241.81	13.93	20.14	242.16	13.42	22.33	64.78	179.43	0.41
6	1	5120.15	5707.71	0.90	210.23	42.93	5.62	202.88	50.63	4.36	54.68	184.38	0.31
7	1	3579.25	4457.56	0.75	147.20	103.63	1.45	203.15	40.82	5.25	24.08	221.25	0.12
8	1	5557.09	3041.31	1.84	229.96	25.58	11.13	232.14	22.21	14.09	82.07	159.71	0.60
9	1	5843.99	6392.60	0.93	213.65	38.58	11.86	236.01	19.03	14.92	27.06	212.46	0.13
10	2	6771.87	2951.36	2.35	222.15	33.17	7.06	246.16	9.21	28.94	66.01	179.73	0.38
11	2	7189.32	4764.02	1.58	110.12	143.58	0.98	157.79	94.02	2.13	150.46	100.07	1.67
12	2	5252.86	5201.68	1.06	161.95	92.67	2.32	242.54	12.80	27.94	112.24	136.26	1.41
13	2	4086.72	6710.96	0.69	174.34	74.25	2.87	201.41	46.82	5.63	70.57	174.09	0.42
14	2	4635.34	2810.58	2.14	212.38	38.30	5.68	197.37	49.51	4.24	30.29	213.01	0.15
15	2	6904.68	3658.95	1.94	241.99	12.85	30.50	242.52	12.13	29.44	75.23	172.39	0.44
16	2												
17	2												

Week # 5 Standing Heart Rate & Blood Pressure Variability

Subject	Group	AR Method			SBP			DBP			RESP		
		LF area	HF area	LF:HF	LF area	HF area	LF:HF	LF area	HF area	LF:HF	LF area	HF area	LF:HF
1	1	6594.01	5133.70	1.82	236.82	18.70	13.46	247.32	8.14	31.97	110.84	121.26	1.00
2	1	4323.13	8635.36	0.53	214.74	37.85	6.63	206.47	46.67	9.29	114.83	130.32	0.98
3	1	3927.20	5110.32	0.85	177.55	74.82	3.48	245.83	9.83	27.96	86.09	165.98	0.61
4	1	6556.50	2743.75	2.37	240.65	13.65	20.11	245.68	8.65	29.48	78.81	166.31	0.56
5	1	5500.49	5240.36	0.90	241.80	13.75	25.16	237.50	17.47	14.57	45.75	197.04	0.24
6	1	5265.06	7422.13	0.71	204.67	47.22	4.68	206.22	40.87	6.82	18.90	225.85	0.09
7	1	7223.84	3908.51	1.82	176.66	68.73	2.83	192.26	51.28	4.03	122.39	115.45	1.15
8	1	6206.31	7746.60	1.02	197.17	53.84	5.20	207.34	44.08	5.08	121.80	120.98	1.04
9	1	5322.36	6563.84	0.82	162.50	87.87	2.56	200.66	52.98	4.17	62.40	182.82	0.39
10	2	6535.76	2976.10	2.23	219.67	35.57	7.25	243.10	12.20	22.86	27.13	223.61	0.13
11	2	6352.65	4203.89	1.54	116.34	135.84	0.97	165.06	87.91	2.22	91.78	156.46	0.60
12	2	5518.26	4302.85	1.30	193.41	61.40	5.91	204.50	49.53	13.86	81.94	167.60	0.62
13	2	5895.34	5371.19	1.20	197.51	56.04	3.58	227.10	26.74	8.65	79.08	168.92	0.49
14	2	6621.08	2940.30	2.32	221.29	32.70	7.17	214.82	38.53	6.08	109.62	133.39	0.85
15	2	6928.39	3677.07	1.96	143.96	101.07	1.47	211.23	40.61	5.51	162.17	89.33	1.91
16	2												
17	2												

Week # 10 Standing Heart Rate & Blood Pressure Variability

Subject	Group	AR Method			SBP			DBP			RESP		
		LF area	HF area	LF:HF	LF area	HF area	LF:HF	LF area	HF area	LF:HF	LF area	HF area	LF:HF
1	1	5888.24	4239.82	1.62	239.98	13.17	28.62	238.62	12.04	29.11	86.65	157.06	0.65
2	1	7157.57	6726.06	1.08	193.84	59.50	3.68	540.12	15.09	21.97	109.28	141.89	0.89
3	1	4354.24	6728.68	0.69	223.73	31.18	9.70	235.23	19.95	13.57	101.43	147.14	0.96
4	1	6743.38	3240.77	2.13	240.32	18.89	14.77	238.34	16.09	21.95	107.58	134.96	0.82
5	1	6237.38	5595.57	1.11	242.74	12.49	21.52	239.25	15.73	17.25	90.90	155.03	0.64
6	1	5471.15	6774.05	0.90	172.07	77.02	2.59	214.33	36.37	7.20	31.80	212.00	0.16
7	1	6008.03	2961.64	2.09	182.54	69.73	3.96	194.01	46.21	4.88	56.07	182.35	0.36
8	1	6155.84	4070.59	1.66	206.47	46.94	4.68	213.19	37.11	6.26	111.99	132.38	0.88
9	1	5650.49	6287.75	0.90	209.73	44.07	5.02	232.34	22.09	12.95	24.09	317.37	0.11
10	2	7491.33	3192.41	2.35	221.62	33.11	6.89	241.20	13.55	17.88	108.83	130.02	0.95
11	2	7171.75	5064.94	1.45	116.55	134.85	1.06	175.89	75.96	2.89	112.22	131.42	0.88
12	2	6060.86	4353.23	1.46	205.82	49.16	4.90	240.65	13.36	20.55	77.13	167.10	0.50
13	2	4196.12	5761.90	0.75	193.35	59.93	4.28	227.15	25.07	9.99	123.72	118.69	1.12
14	2	6800.50	3757.64	1.83	240.21	15.06	17.94	239.20	15.36	18.41	126.98	118.88	1.09
15	2	6436.06	2079.06	3.14	242.99	11.19	38.89	347.14	8.07	40.20	122.67	110.14	1.26
16	2												
17	2												

Average Weekly Maximal Voluntary Contraction (MVC)

Right Hand

Subject	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10
1	96	99	106	100	99	102	102	104	97	95
2	38	37	36	37	36	39	39	39	39	36
3	33	37	33	34	35	33	34	37	36	37
4	64	66	67	69	64	67	68	66	66	66
5	89	96	98	96	99	98	102	99	97	101
6	31	33	29	30	29	28	27	31	33	32
7	59	60	68	68	72	72	76	75	77	94
8	44	44	51	50	50	52	54	53	51	49
9	89	90	90	95	95	89	93	96	87	84

Left Hand

Subject	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10
1	93	96	98	96	95	101	101	101	99	98
2	36	43	41	47	43	46	46	45	48	47
3	23	23	23	28	31	31	31	31	30	30
4	60	59	61	63	60	63	63	65	67	64
5	69	75	78	78	81	92	92	92	91	86
6	31	29	29	32	33	28	28	32	30	34
7	56	67	72	75	74	82	82	82	81	83
8	42	43	48	51	48	42	49	48	46	50
9	83	84	90	87	76	86	86	88	84	76

APPENDIX C:

ANALYSIS OF VARIANCE SUMMARY TABLES

ANOVA Summary Tables

1. Absolute Systolic, Diastolic and Mean Arterial Pressure

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	1064.039	15	739.692	1.4385	0.249
Time (T)	**10**	**214.6219**	**150**	**46.8767**	**4.5784**	**1.1E-05**
G x T	**10**	**158.5086**	**150**	**46.8767**	**3.3814**	**0.0005**

Marked Effects at $p<0.05$

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	**1**	**3217.671**	**15**	**658.397**	**4.8871**	**0.043**
Time (T)	10	37.73599	150	23.8138	1.5846	0.1162
G x T	10	23.47717	150	23.8138	0.9859	0.4582

Marked Effects at $p<0.05$

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	2370.672	15	523.152	4.5315	0.0503
Time (T)	**10**	**71.68091**	**150**	**22.3365**	**3.2091**	**0.0009**
G x T	**10**	**47.63742**	**150**	**22.3365**	**2.1327**	**0.0252**

Marked Effects at $p<0.05$

2. Relative Systolic, Diastolic and Mean Arterial Pressure

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	**1**	**0.16457**	**15**	**0.02228**	**7.3866**	**0.0159**
Time (T)	**9**	**0.007069**	**135**	**0.00192**	**3.6911**	**0.0004**
G x T	**9**	**0.005595**	**135**	**0.00192**	**2.9217**	**0.0034**

Marked Effects at $p<0.05$

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	0.106909	15	0.05595	1.9109	0.1871
Time (T)	9	0.005375	135	0.0032	1.6793	0.0997
G x T	9	0.002513	135	0.0032	0.7852	0.6304

Marked Effects at $p<0.05$

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	**1**	**0.131419**	**15**	**0.02859**	**4.5965**	**0.0488**
Time (T)	**9**	**0.005209**	**135**	**0.00179**	**2.9153**	**0.0035**
G x T	9	0.003079	135	0.00179	1.7233	0.0894

Marked Effects at $p<0.05$

3. Heart Rate Variability LF Area, HF Area and LF:HF Area Ratio

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	21995.36	13	1702732	0.0129	0.9112
Time (T)	**1**	**5107881**	**13**	**1067022**	**4.787**	**0.0475**
G x T	1	641312.4	13	1067022	0.601	0.4521

Marked Effects at $p<0.05$

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	769261.1	13	5118121	0.1503	0.7045
Time (T)	1	342729.4	13	171778	1.9952	0.1813
G x T	**1**	**2579975**	**13**	**171778**	**15.019**	**0.0019**

Marked Effects at $p<0.05$

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	0.028064	13	0.63682	0.0441	0.837
Time (T)	1	0.522998	13	0.11527	4.5373	0.0528
G x T	1	0.296117	13	0.11527	2.569	0.133

Marked Effects at $p<0.05$

4. Systolic Blood Pressure Variability LF Area, HF Area and LF:HF Area Ratio

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	1968.459	13	3515.32	0.56	0.4676
Time (T)	**1**	**8795.237**	**13**	**809.371**	**10.867**	**0.0058**
G x T	**1**	**5805.528**	**13**	**809.371**	**7.1729**	**0.019**

Marked Effects at $p<0.05$

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	6665.631	13	2574.08	2.5895	0.1316
Time (T)	**1**	**3301.594**	**13**	**606.087**	**5.4474**	**0.0363**
G x T	**1**	**5681.371**	**13**	**606.087**	**9.3738**	**0.0091**

Marked Effects at $p<0.05$

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	7.51538	13	17.8996	0.4199	0.5283
Time (T)	1	18.74048	13	19.6004	0.9561	0.346
G x T	**1**	**157.6973**	**13**	**19.6004**	**8.0456**	**0.014**

Marked Effects at $p<0.05$

5. Diastolic Blood Pressure Variability LF Area, HF Area and LF:HF Area Ratio

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	2494.633	13	2078.66	1.2001	0.2932
Time (T)	**1**	**2310.82**	**13**	**441.851**	**5.2299**	**0.0396**
G x T	1	594.268	13	441.851	1.345	0.267

Marked Effects at $p<0.05$

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	1959.078	13	1647.17	1.1894	0.2953
Time (T)	**1**	**2870.648**	**13**	**606.425**	**4.7337**	**0.0486**
G x T	1	2.305205	13	606.425	0.0038	0.9518

Marked Effects at $p<0.05$

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (G)	1	212.313	13	241.142	0.8804	0.3652
Time (T)	1	56.72835	13	95.4744	0.5942	0.4546
G x T	1	21.01933	13	95.4744	0.2202	0.6467

Marked Effects at $p<0.05$

6. Reproducibility of Supine Heart Rate Variability LF Area, HF Area and LF:HF Area Ratio

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Test Day	2	987109.9	10	463912	2.1278	0.1699

Marked Effects at $p<0.05$

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Test Day	2	304559.2	10	557566	0.5462	0.5955

Marked Effects at $p<0.05$

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Test Day	2	0.009362	10	0.10934	0.0856	0.9186

Marked Effects at $p<0.05$

7. Reproducibility of Standing Heart Rate Variability LF Area, HF Area and LF:HF Area Ratio

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Test Day	2	559780.4	10	527101	1.062	0.3817

Marked Effects at $p<0.05$

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Test Day	2	305746	10	347573	0.8797	0.4447

Marked Effects at $p<0.05$

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Test Day	2	0.065152	10	0.11879	0.5485	0.5943

Marked Effects at $p<0.05$

8. Supine versus Standing Reproducibility of Heart Rate Variability LF Area, HF Area and LF:HF Area Ratio

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Position (P)	1	5865911	10	2357023	2.4887	0.1457
Time (T)	2	87572.38	20	495507	0.1767	0.8393
P x T	2	1459318	20	495507	2.9451	0.0757

Marked Effects at $p<0.05$

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Position (P)	1	6827824	10	5168380	1.3211	0.2771
Time (T)	2	601998.3	20	452569	1.3302	0.2868
P x T	2	8306.907	20	452569	0.0184	0.9818

Marked Effects at $p<0.05$

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Position (P)	1	1.767677	10	1.26421	1.3982	0.2644
Time (T)	2	0.019123	20	0.11407	0.1676	0.8468
P x T	2	0.055391	20	0.11407	0.4856	0.6224

Marked Effects at $p<0.05$

9. Maximal Voluntary Contraction for Right Hand and Left Hand

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Time	9	31.16173	72	16.2173	1.9215	0.0622

Marked Effects at $p<0.05$

Effect	df Effect	MS Effect	df Error	MS Error	F	p-level
Time	**9**	**95.65556**	**72**	**15.9306**	**6.0045**	**3E-06**

Marked Effects at $p<0.05$