THE EFFECTS OF SIX WEEKS OF ISOMETRIC HANDGRIP TRAINING ON BLOOD PRESSURE, THE AUTONOMIC NERVOUS SYSTEM AND ARTERIAL STIFFNESS IN NEWLY DIAGNOSED HYPERTENSIVES.

THE EFFECTS OF SIX WEEKS OF ISOMETRIC HANDGRIP TRAINING ON BLOOD PRESSURE, THE AUTONOMIC NERVOUS SYSTEM AND ARTERIAL STIFFNESS IN NEWLY DIAGNOSED HYPERTENSIVES

By

MELANIE I. STUCKEY, B.Sc.

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AUTHOR:	Melanie I. Stuckey, B.Sc. (University of Western Ontario)
SUPERVISOR:	Dr. Neil McCartney, Ph.D.
SUPERVISORY COMMITTEE:	Dr. Markad V. Kamath, Ph.D., P.Eng. Dr. Gina Agarwal, MBBS, MRCGP, CCFP, Ph.D. (Cand) Dr. Doug Oliver, MSc, MD, CCFP
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ABSTRACT

Supervised isometric handgrip training (IHG) has been shown to lower blood pressure (BP) and therefore, may be an effective non-pharmacological treatment for hypertension. The present investigation examined the efficacy of unsupervised IHG to lower BP in patients who were recently diagnosed as hypertensive. Since the mechanisms responsible for attenuating BP remain unclear, this study also investigated the concurrent effects of IHG training on the autonomic nervous system (ANS) and arterial stiffness.

Eight participants were randomized to the experimental group and the remaining six served as controls. Lifestyle modifications to lower BP were recommended for both groups. In addition, the experimental group completed IHG three times per week for six weeks. IHG consisted of four two-minute isometric contractions at 30% maximal voluntary contraction using alternate hands, each separated by a one-minute rest period. Pre- (PRE) and post-intervention (POST), BP was measured and the ANS was assessed by baroreceptor sensitivity (BRS) and both systolic and diastolic blood pressure variability (SBPV and DBPV) and arterial stiffness was evaluated by carotid-finger pulse wave velocity (PWV). All measures were assessed during a period of supine rest and during a 60° passive tilt.

There were no significant changes in any BP measure from PRE to POST for either the experimental or control groups. There was a non-significant trend toward decreased heart rate ($p = 0.065$). BRS decreased from PRE to POST in

both the experimental (10.7 ± 2.4 mm Hg to 9.7 ± 2.3 mm Hg) and control groups (8.6 ± 2.1 mm Hg to 7.6 ± 1.5 mm Hg), but there was no difference between groups. SBPV LF:HF was lower at POST than PRE in both experimental (6.8 ± 1.5 to 4.6 ± 1.1) and control (3.4 ± 1.9 to 2.3 ± 0.9), but there were no other differences in any other BPV variable. There were no significant changes in PWV.

In conclusion, unsupervised IHG did not lower resting BP in newly diagnosed hypertensive patients, so there were no improvements in autonomic indices. There was a decrease in SBPV LF:HF indicating improved sympathovagal balance, but this was likely a result of lifestyle modification rather than IHG. Future studies are necessary to determine appropriate use of IHG as a treatment for hypertension and to verify the mechanisms responsible for BP attenuation with IHG.

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TABLE OF CONTENTS

List of Figures **Page**

List of Tables **Page**

List of Abbreviations

Angiotensin Converting Enzyme	ACE
Angiotensin II	Ang II
Area Under the Curve	AUC
Autonomic Nervous System	ANS
Baroreceptor Sensitivity	BRS
Baroreceptor Sensitivity – All Rising and Lowering	BRS-A
Baroreceptor Sensitivity – Lowering	BRS-L
Baroreceptor Sensitivity – Rising	BRS-R
Blood Pressure	BP
Blood Pressure Variability	BPV
Diastolic Blood Pressure	DBP
Diastolic Blood Pressure Variability	DBPV
Electrocardiogram	ECG
Heart Rate	HR
Heart Rate Variability	HRV
High Frequency	HF
Isometric Handgrip Training	IHG
Low Frequency	LF
Maximal Voluntary Contraction	MVC
Mean Arterial Pressure	MAP
Millimetres of Mercury	mm Hg
Muscle Sympathetic Nerve Activity	MSNA
Nitric Oxide	NO
Parasympathetic Nervous System	PNS
Pulse Transit Time	PTT
Pulse Wave Velocity	PWV
Reactive Oxygen Species	ROS
Renin Angiotensin System	RAS
RR interval	RRi
Standard Error of the Mean	SEM
Sympathetic Nervous System	SNS
Systolic Blood Pressure	SBP
Systolic Blood Pressure Variability	SBPV
Transit Time	TT
Very Low Frequency	VLF

1.0 INTRODUCTION

1.1 The Autonomic Nervous System

The autonomic nervous system (ANS) is essential for proper control of the cardiovascular system both at rest and during exercise. The ANS contributes to the maintenance of cardiovascular homeostasis and reacts to stressors and other stimuli with hormonal and neural responses (Franchini and Cowley, 2004a). The neural component of the ANS is divided into two sections: 1) the parasympathetic nervous system (PNS) and 2) the sympathetic nervous system (SNS). Vastly simplified, the SNS is responsible for preparing the body for and reacting to stressors, while the PNS returns the system to its resting state (Franchini and Cowley, 2004a). However, both systems are constantly engaged and a number of complex interactions are involved in cardiovascular control (Franchini and Cowley, 2004a). The ANS controls the cardiovascular system by innervating the heart and blood vessels, ultimately to maintain blood pressure (BP).

1.2 Blood Pressure

Arterial BP is the force that blood exerts on the arteries. Systolic BP (SBP) is measured when the heart pumps blood, and diastolic BP (DBP) occurs when the heart is relaxed. Mean arterial pressure (MAP) is the average pressure exerted on the arterial walls and is calculated as one third of SBP plus two-thirds DBP (Marieb, 2005). This is in accordance with the relative time spent in systole

and diastole during each heart cycle. BP is the product of cardiac output, which is affected by heart rate (HR) and stroke volume, and total peripheral resistance, which is determined by vascular tone (Marieb, 2005) (Equations 1.1 and 1.2).

Blood Pressure = Cardiac Output x Total Peripheral Resistance (Equation 1.1)

Cardiac Output = Heart Rate x Stroke Volume (Equation 1.2)

A number of physiological factors influence blood pressure including the nervous system, local endothelial factors, intrinsic myogenic factors and the renin-angiotensin system. Optimal BP control is dependant upon the complex interplay between these regulators.

1.3 Neural Regulation: The Baroreflex

The baroreflex is a typical negative feedback loop and is considered to be the primary mechanism responsible for the short-term control of BP. Arterial baroreceptors are clusters of specialised nervous tissue located in the carotid sinus and aortic arch (Silverthorn, 2001). Afferent nerves run to the medulla oblongata in the brain stem where the reflex synapses and efferent signals are sent to the heart and blood vessels to alter HR, vasoconstriction, venoconstriction and cardiac contractility to maintain BP at appropriate levels (Bristow *et al.*, 1969; La Rouvere *et al.*, 1995) (Figure 1.1). Baroreceptors increase their firing rate in response to stretching of the arteries, and decrease their firing rate when the arteries become less stretched. In a healthy individual, the amount of mechanical distortion of the arteries is usually related to the magnitude of pressure change

(LaRouvre *et al.*, 1995). Therefore, high BP stretches the arteries, which signals a chain of events to decrease BP and visa versa.

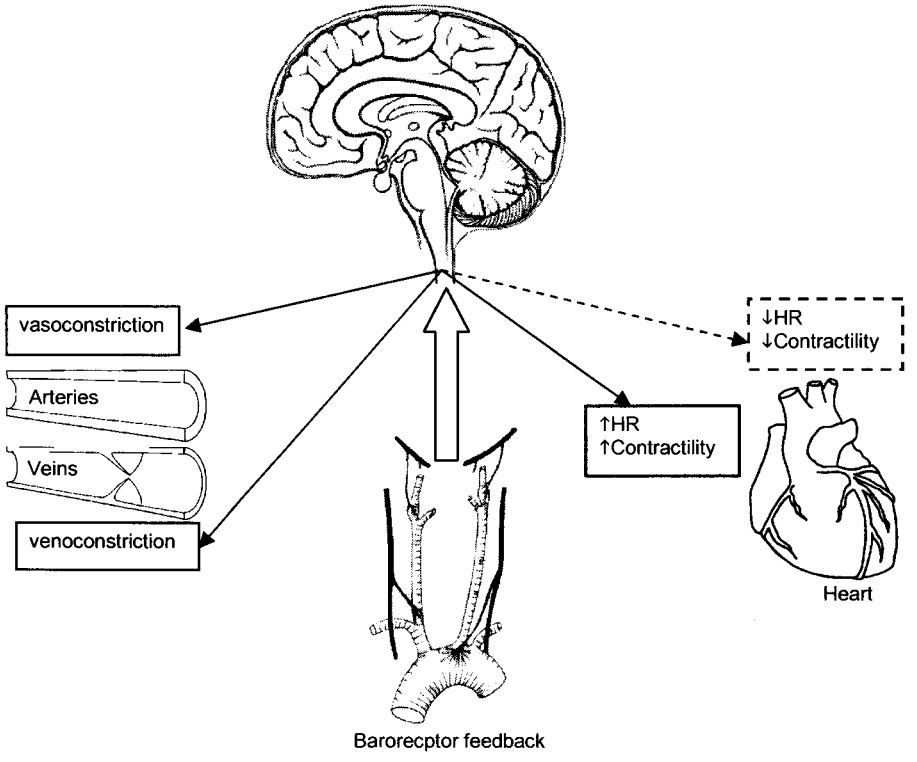

Figure 1.1: Baroreceptor control of the heart and blood vessels via the parasympathetic (dashed line) and sympathetic (solid line) nervous systems.

Some situations, such as exercise, require BP to be maintained at higher levels. Current evidence suggests that BP increases at the onset of exercise are due to a "resetting" of the baroreflex. In this situation, normal resting BP is perceived as relative hypotension, or low BP, and the ANS responds by increasing BP (Rowell, 1993). One mechanism that might be responsible for resetting the baroreflex is the muscle metaboreflex (Rowell and O'Leary, 1990). The afferent

arm of this reflex is composed of group III and IV myelinated and unmyelinated nerve fibres that respond to increased concentrations of blood metabolites by increasing blood flow, which results in augmented BP (Rowell and O'Leary, 1990). Motor outflow from the cerebral cortex, termed central command, may also be involved in resetting the baroreflex (Rowell, 1993). Available evidence suggests that central command is likely responsible for the immediate withdrawal of vagus innervation upon commencement of exercise, and that the metaboreflex is important in modulating the slower sympathetic response (Rowell and O'Leary, 1990).

1.3.1 Parasympathetic Branch of the Baroreflex

The parasympathetic branch of the baroreflex innervates the heart via the vagus nerve. Upon stimulation, vagal nerves release the neurotransmitter acetylcholine. When acetylcholine binds with muscarinic receptors on the heart, it results in bradycardia, or a slower HR, and decreased contractility, thus decreasing BP (LaRouvre *et al.*, 1995). This system is quick to respond and changes HR within a single beat (Franchini and Cowley, 2004*a*).

Parasympathetic motoneurons are modulated by systolic pressure (Rudas *et al.*, 1999); thus, the cardiovagal baroreflex curve (Figure 1.2) is determined by the sigmoidal relationship between SBP and RR interval, or the time between electrocardiogram (ECG) R-spikes (Eckberg, 2004). Along the linear portion of the curve is an operating point, which corresponds to resting BP. Deviations from

the operating point result in changes in RR interval (RRi) with greater changes around the operating point and lesser changes at either of the extremes. The cardiovagal baroreflex demonstrates hysteresis, with greater RR interval responses to increasing BP than to decreasing BP (Rudas *et al.*, 1999).

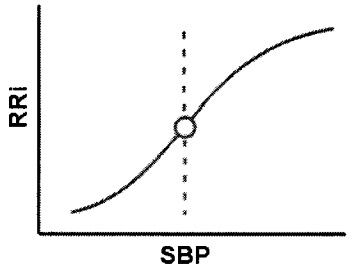

Figure 1.2: Cardiovagal baroreflex curve. "O" is the operating point. (Eckburg, 2004).

1.3.2 Sympathetic Branch of the Baroreflex

The SNS innervates both the heart and blood vessels, causing increased heart rate and contractility, and arterial vasoconstriction, thus increasing blood pressure. Norepinephrine, the main neurotransmitter associated with the SNS (Franchini and Cowley, 2004*a*), binds with beta-adrenergic receptors in the heart and both beta- and alpha-adrenergic receptors on the vessels. The SNS is slower to respond than the PNS, taking two to three seconds to begin, and up to thirty seconds to reach a steady state (Franchini and Cowley, 2004*a*). This branch is responsible for regulating baseline vascular tone (Franchini and Cowley, 2004*b*; LaRouvre *et al.*, 1995), as there is a constant discharge of sympathetic impulses from the pressor centre to maintain some degree of baseline vasoconstriction (LaRouvre *et al.*, 1995).

Sympathetic motoneurons are inhibited by baroreceptor firing (O'Leary *et al.*, 2003; Rudas *et al.*, 1999). Once baroreceptor activity ceases, sympathetic activation resumes and is inversely related to DBP (O'Leary *et al.*, 2003; Rudas *et al.*, 1999). Therefore, the sympathetic baroreflex curve (Figure 1.3) results from a reverse sigmoid relationship between DBP and muscle sympathetic nerve activity (MSNA). Similar to the cardiovagal reflex, the sympathetic curve also has an operating point on the linear portion of the curve, although it is only slightly below the threshold for sympathetic activation (Eckberg, 2004). This branch of the baroreflex does not demonstrate hysteresis, as it exhibits similar MSNA responses to rising and falling BP (Rudas *et al.*, 1999).

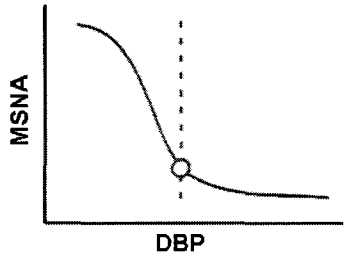

Figure 1.3: Sympathetic baroreflex curve. "O" is the operating point. (Eckburg, 2004).

1.3.3 Sympathovagal Balance

The balance between the PNS and SNS influences BP and the vagal influence on the heart opposes sympathetic effects (Franchini and Cowley, 2004*a*). In healthy, resting individuals, there is a greater amount of vagal than sympathetic activity. This ratio changes with disease, exercise and other stressors, which favour greater sympathetic activity. The effects of both systems

are not simply additive as acetylcholine from the PNS decreases the effectiveness of norepinephrine and possibly visa versa (Franchini and Cowley, 2004*a*).

1.4 Measuring the Baroreflex

Baroreceptor sensitivity (BRS) is an integrative measurement of autonomic control, which acts as an index of reflex vagal or sympathetic activity (Pitzalis *et al.*, 1998). Cardiovagal BRS is expressed in Δms / Δmm Hg and reflects the ability of the heart to respond to fluctuations in BP. Sympathetic BRS is expressed as ΔMSNA (au) / Δmm Hg and reflects the ability of the SNS to respond to BP changes. Both types of BRS measurements can be taken under natural conditions to investigate spontaneous reflexes, or with the application of external stimuli to examine heart period or sympathetic outflow responses to exaggerated changes in BP.

1.4.1 External Stimulus Methods

1.4.1.1 Pharmacological Method

The Oxford method was first described by Smyth *et al.* (1969) and involves the administration of an angiotensin bolus intravenously to elicit a drastic increase in BP. The increase in RRi that occurs in response is graphed against the change in BP and the regression of the slope is taken to be the BRS. This method has been since modified to consist of the phenylephrine bolus to increase BP followed by a bolus of nitroprusside to reduce BP and visa versa (Rudas *et al.*,

1999). The modified Oxford method allows for characterization of both rising and lowering BRS. This method is generally considered to be the "gold standard" for measuring BRS.

1.4.1.2 Neck Suction and Pressure

This method involves a malleable lead collar that encircles the anterior and lateral aspects of the neck and applies pressure and suction to the neck and therefore, the carotid arteries (Fadel *et al.*, 2003). It is assumed that the change in transmural pressure of the carotid arteries provides a direct stimulus to the baroreceptors (Fadel *et al.*, 2003; Hitz and Dütsch, 2006; LaRouvre *et al.*, 1993). When neck pressure is applied, transmural pressure increases, simulating hypotension (low BP), while the application of neck suction simulates hypertension (high BP) (Diaz and Taylor, 2006; Fadel *et al.*, 2003; LaRouvre *et al.*, 1995). A complete baroreflex curve can be created from this test.

1.4.2 Spontaneous Methods

1.4.2.1 Sequence Method

The sequence method is a non-invasive method used for assessing BRS in the time domain. Sequences of at least three beats where BP consecutively increases or decreases are regressed against corresponding lengthening or shortening of the RRi (Kardos *et al.*, 2001). The slope of the regression line is taken as the BRS. Conventionally, SBP is used in this measure, thus reflecting the vagal baroreflex (Kardos *et al.*, 2001). Analysis in our lab has found that

sequences involving RR interval and DBP exist, however, there are generally fewer of these sequences than SBP. It is unknown whether or not a relationship exists between RR interval and DBP and whether or not this potential relationship is reflective of some physiological variable.

The sympathetic baroreceptor sensitivity is measured in a similar fashion, but with sequences of increasing DBP related to increases in burst frequency of MSNA (O'Leary *et al.*, 2003). Microneurography is a technique for recording sympathetic outflow, in which MSNA is collected by inserting a microelectrode into a superficial nerve. Sympathetic nerve activity causes "bursts" in the readout, with a higher amplitude or higher frequency of bursts indicating greater activation (O'Leary *et al.*, 2003).

1.4.2.2 Spectral Method

The cardiovascular system is constantly changing as demonstrated by graphing beat-by-beat RRi or BP over time. These graphs can be decomposed with spectral methods to analyse underlying rhythmic components (Figure 1.4).

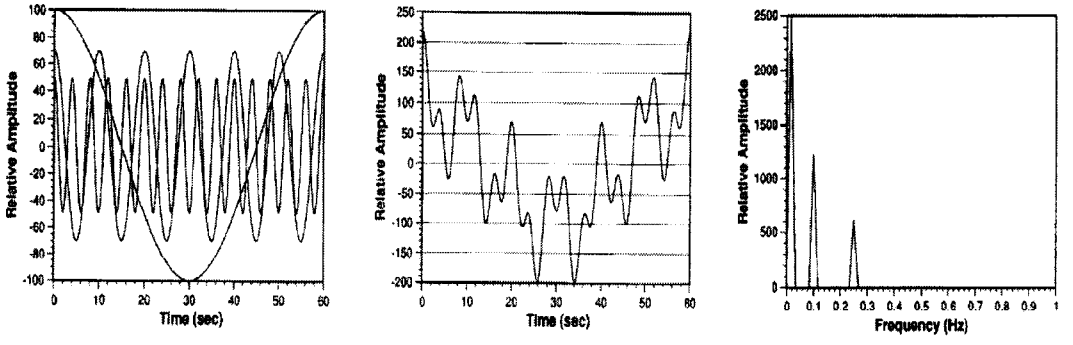

Figure 1.4: Left: three sinusoidal signal: 1Hz, 6Hz, 15Hz superimposed on the same scale. Centre: same tree signals combined into one signal. Right: Power spectral analysis of signal shown in centre. (Stein *et al.*, 1994)

The amplitude of RRi oscillations is divided by the amplitude of corresponding BP oscillations, and the square root of the ratio is taken as the BRS, provided that a coherence greater than 0.05 is obtained (La Rouvere *et al.*, 1995) The band that occurs with a frequency of approximately 0.1 Hz in humans is most commonly analysed. These waves are called Mayer waves, and are thought to be directly related to baroreflex function (Julien, 2006; Pagani *et al.*, 1988; Takalo *et al.*, 1999).

1.4.3 Spontaneous versus Externally Stimulated Methods

Spontaneous methods examine BRS in a natural environment, which examines heart period or MSNA responses to small changes in BP. It is likely that some of the sequences and relationships examined in this analysis occur by chance rather than baroreflex influence (Diaz and Taylor, 2006). Alternatively, methods using external stimulation force a constant increase or decrease of the BP signal to the baroreceptors without allowing feedback to counteract BP changes (Diaz and Taylor, 2006). This allows for examination of how well the HR reacts to large pressure changes, which means that changes are likely not random. However, it examines responses to stimuli that are rarely, if ever, encountered in the natural environment.

At rest, pharmacological methods have been shown to be highly correlated to spontaneous methods, but show poor correspondence (Dias and Taylor, 2006; Pitzalis *et al.*, 1998), with tests using vasoactive drugs eliciting lower BRS values

than spontaneous methods (Pitzalis *et al.*, 1998). Differences between spontaneous and externally influenced baroreflex curves may arise because the baroreflex is responsible for both the long-term and short-term regulation of BP (LaRouvre *et al.*, 1995). Therefore, the pharmacological method may be appropriate for describing short-term regulation of BP, as external stimulation results in acute rises in BP, while the spontaneous methods may be reflective of long-term regulation, as these techniques examine the baroreflex under natural conditions (LaRouvre *et al.*, 1995).

1.5 Other Blood Pressure Regulators

1.5.1 Endothelial Factors

The endothelial layer is capable of producing a number of vasodilatory compounds. Nitric oxide (NO) is a potent vasodilator that is released locally from the arterial endothelium in response to shear stress (Marieb, 2005). It is thought to be important in BP regulation to open vessels and keep BP at a lower level.

1.5.2 Myogenic Factors

Calcium causes contraction of the smooth muscle lining of the artery. Calcium enters the cell during depolarization, when the cell membrane is mechanically distorted, and when the cell is stimulated by a neurotransmitter or other chemical (Silverthorn, 2001). Influx of extracellular calcium into the cell triggers the release of intracellular calcium from the sarcoplasmic reticulum of the

smooth muscle. Calcium is involved in a number of processes, which ultimately result in the formation of the actin-myosin cross-bridge and smooth muscle contraction (Silverthorn, 2001).

1.5.3 Renin-Angiotensin System

The renin angiotensin system (RAS) influences long-term BP regulation by controlling fluid levels in the body. When BP falls, the kidneys release an enzyme called renin into the blood stream. Renin initiates a number of reactions ultimately leading to the conversion of Angiotensin I to Angiotensin II (Ang II) by the Angiotensin Converting Enzyme (ACE). Ang II is a potent hormone that causes vasoconstriction, which increases BP (Silverthorn, 2001). Ang II also signals the release of aldosterone, a hormone that causes sodium retention in the kidney (Silverthorn, 2001). Thus, less water is excreted from the body, which results in an increase in blood volume and pressure.

In addition, Ang II interacts with the ANS by facilitating the SNS and impeding the PNS (Diz and Averill, 2004). Ang II also directly affects the baroreflex by attenuating its ability to withdraw sympathetic signals to the heart and vasculature in response to increased BP (Diz and Averill, 2004).

1.6 Measuring the Autonomic Nervous System

1.6.1 Cardiovascular Variability

As mentioned above, the cardiovascular system is a dynamic system. The variability that exists in the system is thought to be a marker of autonomic function. Cardiovascular variability can be examined in either the time domain via statistical analysis or the frequency domain via spectral analysis. Time domain analysis uses calculations such as standard deviations and proportions to characterise variability based on interbeat intervals and on comparisons of lengths of adjacent cycles (Stein *et al.*, 1994; Stein and Kleiger, 1999). Essentially, it describes the amount of existing variability. Frequency domain analysis decomposes the haemodynamic signal into a series of sine and cosine waves of different frequencies, each of which gives information about different physiological parameters (Kamath and Fallen, 1993). Changes in cardiovascular variability have been associated with advancing age (Bonnemeier *et al.*, 2003; Laitinen *et al.*, 2004; Piccirillo *et al.*, 1995) and a number of pathologies including hypertension and associated diseases such as coronary heart disease (Kamath and Fallen, 1993; Stein and Kleiger, 1999) and diabetes (Kamath and Fallen, 1993; Loimaala *et al.*, 2003).

1.6.2 Heart Rate Variability

Heart rate variability (HRV) is a non-invasive method used to assess autonomic function (Freeman, 2006; Hitz and Dütsch, 2006; Kamath and Fallen,

1993) by providing an index of the cardiac vagal tone (Freeman 2006; Pitzalis *et al.*, 1998). Healthy individuals have a high HRV, enabling them to respond quickly to changes in BP. Electrocardiography (ECG) is used to collect heart period measures over time and changes in the RRi are analysed. Frequency specific oscillations in heart period signals are related to distinct autonomic functions. High frequency (HF) oscillations are those between 0.15 and 1.4 Hz, and are unequivocally considered to be a marker of parasympathetic function (Task Force, 1996). The low frequency (LF) band is between 0.04 and 0.15 Hz and controversy exists regarding whether it reflects purely sympathetic function, or whether it contains input from both the SNS and PNS (Task Force, 1996). The ratio of the low and high frequencies (LF:HF) is generally considered to be a measure of sympathovagal balance (Taylor *et al.*, 2003). Time domain measures have also been shown to reflect the activities of the ANS.

1.6.3 Blood Pressure Variability

Blood pressure variability (BPV) is considered an index of vasomotor tone. Since the primary purpose of the cardiovascular system is to maintain blood pressure, healthy individuals show lower BPV, reflecting the ability of the system to quickly react to stimuli to keep BP relatively stable. Like HRV, BPV is measured in both the time and frequency domain. BPV in the time domain is usually calculated from readings from 24-hour ambulatory BP monitoring and

characterised by the standard deviation of both SBP and DBP (Mancia *et al.*, 2007; Verdecchia *et al.*, 2007).

Studies have found that BPV frequencies may relate to different BP regulatory systems. There is strong evidence relating BPV LF (0.075-0.15 Hz) directly to the arterial baroreflex influence on sympathetic modulation of vascular tone (Parati *et al.*, 1995; Strauss, 2007). The endothelial NO system may also contribute to the LF frequency, though this remains controversial (Castellano *et al.*, 1995; Cooke *et al.*, 2002b).

Very low frequency (VLF) (0.02 - 0.07 Hz) of BPV is thought to be related to intrinsic myogenic function (Strauss, 2007), to the RAS control of BP (Parati *et al.*, 1995; Strauss, 2007), and possibly to thermoregulatory processes or endothelial factors (Parati *et al.*, 1995). Calcium channel blockade significantly decreased VLF and LF in rats, though the reduction in LF was thought to be from a reduction in sympathetic activity (Strauss, 2007). Although research is thus far inconclusive, myogenic factors may influence both the VLF and LF in humans (Strauss, 2007). The RAS is considered to contribute to BPV VLF based primarily upon the operating speed of the system (Strauss, 2007), since renin and angiotensin must be synthesized and released before exerting control over the circulatory system.

Little is known about the HF range of BPV. It is thought that, like HRV HF, BPV HF may also be strongly linked to respiration (Parati *et al.*, 1995; Strauss, 2007) or other mechanical factors since HF power is not modified in

patients with a denervated donor heart (Parati *et al.*, 1995). However, consensus has not yet been reached. Castellano and colleagues (1995) found an association between endothelial NO and BPV HF, with NO synthase inhibition augmenting BPV HF. However, since respiration was not controlled, it is unknown whether the effects are purely due to changes in NO regulation of BP or whether changes in respiration are responsible for the changes in BPV HF.

1.6.4 Orthostatic Challenge

An orthostatic challenge is one way of challenging the autonomic nervous system to investigate the dynamic regulation of BP (Laitinen *et al.*, 2004), which may reveal information that cannot be seen under resting conditions (Ueno *et al.*, 2003). Two common challenges are: 1) active standing, where one goes from the supine to the standing position and then stands quietly for a period of time; and 2) tilt testing, where one lies on a mechanical table that can be tilted between zero and ninety degrees. During the orthostatic challenge, gravity causes blood to move to the lower extremities, unloading the baroreceptors and causing a change in the afferent input to the cardiovascular centres in the brain (Rowell, 1993; Ueno *et al.*, 2003). When movement takes place, the muscle pump in the legs assists the return of blood to the heart and brain. With the absence of these movements, the neural system must react to constrict the blood vessels and return blood to the heart. Active standing is advantageous because it requires no additional equipment; however, the muscular contractions of the abdominal and

leg muscles involved in standing introduce another factor besides the ANS, which may confound results (Hilz and Dütsch, 2006). Tilt testing is easy to administer and if kept to 60° or less, muscular contractions can generally be avoided (Freeman, 2006; Hilz and Dütsch, 2006).

Autonomic indices are often measured during an orthostatic challenge. Cardiovascular variability should reveal a sympathovagal balance with greater PNS than SNS input at rest and increasing LF and decreasing HF upon standing or tilting (Lewis, 2005). In healthy individuals, BRS decreases during a standing challenge (Stuckey *et al.*, 2007), but the ANS may react differently to this stress in disease states.

1.7 Hypertension

High BP, or hypertension is the leading risk factor for heart attack, stroke, congestive heart failure and kidney failure (Östergren, Kanavos and Weber, 2007; World Health Organisation/International Society of Hypertension, 2003). There are two main types of high BP: 1) Essential hypertension, a disease of unknown etiology in which resting BP is consistently elevated above normal values (Maver, Strucl and Accetto, 2004; Pagani and Luchini, 2001) and 2) Secondary hypertension, which occurs due to a causal pathology, such as renal disease (Grassi *et al.*, 1998). Since the latter will resolve once the underlying disease is cured, the remainder of this review will focus on essential hypertension. The Joint National Committee on prevention, detection, evaluation and treatment of

high blood pressure (2003) has set guidelines that classify BP as healthy, borderline, or pathological (Table 1.1). A physician will diagnose their patient as hypertensive if BP is elevated for three consecutive visits (Joint National Committee, 2003). A phenomenon known as "White Coat hypertension" occurs when patients have consistently elevated BP readings in the physician's office, but normal ambulatory BP (Pickering *et al.*, 2005).

Table 1.1 Classification of blood pressure for adults. (Joint National Committee, 2003)

BP Classification	SBP (mm Hg)	DBP (mm Hg)
Normal	<120	And <80
Pre-Hypertension	120-139	Or 80-89
Stage 1 Hypertension	140-159	Or 90-99
Stage 2 Hypertension	≥ 160	Or ≥ 100

1.7.1 Hypertension and the Autonomic Nervous System

Essential hypertension is associated with impairment of the ANS (Maver, Strucl and Accetto, 2004). It is well established that high BP is associated with a decrease in BRS (Bristow *et al.,* 1969; Kardos, *et al.*, 2001). Hypertensives show sympathetic over-activity demonstrated by increased MSNA (Grassi *et al.*, 1998), increased BPV LF power (Pagani and Lucini, 2001) and increased HRV LF power (Piccirillo *et al.*, 1996; Piccirillo *et al.*, 2006) when compared with normotensive subjects. MSNA responses to tilt are also exaggerated in pre-hypertensives (Rea and Hamdan, 1990), and BPV LF values are higher in hypertensives than in normotensives during "white coat" BP measurements, standing, and mental arithmetic (Lantelme *et al.*, 1998). The increase in sympathetic function is usually paired with a decrease in parasympathetic

function as demonstrated by a diminished HRV HF power (Liao *et al.*, 1996). Taken together, this means that altered sympathovagal balance is associated with elevated BP.

Discrepancy exists regarding whether ANS dysfunction is a cause or a result of hypertension. Normotensive subjects with a family history of hypertension may be studied as pre-hypertensives. Since hypertension has a genetic component, it is assumed that early pathologies leading to the disease may already be present in this population. It has been demonstrated that these subjects show lower BRS than a comparable population without a family history of hypertension (Maver, Strucl and Accetto, 2004). However, Grassi *et al.* (1998) concluded that since changes in the baroreflex occur in both essential and secondary hypertension, changes in the ANS are more likely the sequelae of the disease, rather than the cause. In rats, sympathetic activity increases with the development of hypertension, but drops back to normal values during sustained hypertension (Nagai *et al.*, 2003). Whether or not the development of hypertension follows the same process in humans is unknown.

While autonomic dysregulation is a probable cause of hypertension, interactions of other regulatory systems with the baroreflex may contribute to the increase in resting BP. For example, Ang II has been found to reduce BRS by inhibiting the ability of the vagal arm to adjust HR in response to BP fluctuations (Diz and Averill, 2004).

1.7.2 Arterial Stiffness

Arterial stiffness has become recognised as a major risk factor for increased SBP, pulse pressure (O'Rourke and Staessen, 2002) and cardiovascular diseases (Laurent *et al.*, 2006) including hypertension (Khoshdel *et al.*, 2006). Arteries are composed of collagen, elastin and smooth muscle. In healthy individuals, the arteries stretch as the pressure wave moves along the vessel to minimise the wave reflection (Laurent *et al.*, 2006; O'Rourke and Staessen, 2002). In stiff arteries, the reflection of the pressure wave is additive to the systolic wave, resulting in increased SBP (Laurent *et al.*, 2006; O'Rourke and Staessen, 2002; Pickering *et al.*, 2005). Arterial stiffness in the carotid arteries may result in further increases in BP by decreasing BRS. Since the baroreceptors respond to arterial distortion rather than to pressure changes *per se* (Eckburg, 2004), changes in arterial compliance that occur with aging or certain pathologies may be responsible for the dysregulation of BP. Steinback and colleagues (2005) examined the relationship between cardiovagal BRS and carotid distensibility, a measure related to arterial stiffness. In healthy individuals, they found no relationship between the changes in carotid distensibility and those in cardiovagal BRS during a 60° head up tilt. However, in chronic haemodialysis (Chesterton *et al.*, 2005) and stroke patients (Eveson *et al.*, 2005), a significant relationship has been found between decreased BRS and arterial stiffness under resting conditions.

1.7.2.1 Measuring Arterial Stiffness

Pulse wave velocity (PWV) is a simple, non-invasive method for measuring arterial stiffness (Laurent *et al.*, 2006; O'Rourke and Staessen, 2002) that has proved to be robust and reproducible (Laurent *et al.*, 2006). PWV (m/s) is calculated from the distance between two pulse sites and the pulse transit time (PTT). Although any two sites in relatively linear arrangement can be used, carotid-femoral PWV is considered to be the gold-standard measurement of arterial stiffness (Laurent *et al.*, 2006; Tillin *et al.*, 2007). The time lag between the R spike from an ECG recording and the foot of the BP wave (Raggi *et al.*, 2007), immediately prior to the steep rise of the wave front (Laurent *et al.*, 2006) is calculated for each pulse site. The difference between these times is the PTT (Laurent *et al.*, 2006; Raggi *et al.*, 2007). PWV is calculated from the difference between the distance to the distal and proximal sites from the heart, or sternal notch, divided by the PTT (Equation 1.3).

PWV = (distal distance – proximal distance) / (distal time – proximal time)

(Equation 1.3)

Applanation tonometry is one method used to record wave form for PWV analysis. As the name suggests, applanation tonometry works by flattening an artery between a bone or other solid structure and the tonometer (Matthys and Verdonck, 2002; Pickering *et al.*, 2005). Pressure changes are sensed through a high-fidelity transducer and a pressure-time wave is produced (Matthys and Verdonck, 2002). This method is sensitive to observer hold-down pressure, so

calibration with a cuff measurement is necessary if absolute values are used. However, this method is best used for waveform analysis rather than measurement of absolute BP values. This method is also sensitive to positioning and motion (Matthys and Verdonck, 2002), so it is useful only under resting conditions.

1.7.3 Disease Burden

Hypertension is a major health problem, affecting one quarter of the world's adult population (Östergren, Kanavos and Weber, 2007). It is a major risk factor for cardiovascular and renal diseases (Östergren, Kanavos and Weber, 2007; World Health Organisation/International Society of Hypertension, 2003), thus contributing to a substantial amount of overall morbidity and mortality. Hypertension places a significant burden on the health care system since more than 50% of the elderly are hypertensive (Östergren, Kanavos and Weber, 2007; World Health Organisation/International Society of Hypertension, 2003) and pharmacological treatment often requires a combination of at least two (Joint National Committee, 2003) or three different drugs (World Health Organisation/International Society of Hypertension, 2003). Thus, to reduce the financial burden, it is becoming increasingly important to promote cost effective methods to treat hypertension.

1.7.4 Pharmacological Treatment of Hypertension

As discussed above, there are a number of pathways involved in BP regulation. Pharmacological treatment targets one or more of these pathways to decrease BP. Beta-blockers have antagonistic effects on beta-adrenergic receptors, thus blunting the effects of the SNS on the heart and blood vessels. ACE inhibitors prevent the conversion of angiotensin I to Ang II, resulting in better regulation of blood volume. Diuretics are also used to reduce water retention. Calcium blockers restrict entry of calcium into the cell, which relieves tonic vasoconstriction by reducing smooth muscle contraction.

Non-adherence to pharmacologic treatment is a common problem (Östergren, 2007). It is estimated that over 50% of patients do not follow their prescribed treatment plan (Östergren, 2007). This could be due to a number of factors including miscommunication between the patient and health care professional, lack of motivation or support from family and friends, or the choice not to take medications because of the plethora of adverse side effects associated with many pharmacological treatments. It is possible that alternative treatments would be more cost effective, and perhaps more palatable for the patient, which may result in improved adherence.

1.7.5 Lifestyle Modifications to Treat Hypertension

There are a number of modifiable risk factors for hypertension including, obesity, high dietary sodium intake, smoking, stress, and physical inactivity

(Östergren and Kanavos, 2007). Therefore, interventions aimed at modifying these factors, including dietary changes, smoking cessation, relaxation and exercise may reduce the burden on the health care system by treating hypertension non-pharmacologically. If promoted to normotensive individuals, the cost may be reduced further by preventing disease development. Currently, literature available to patients recommends a diet low in salt and high in fruits and vegetables to increase fibre intake. Researchers have found that inclusion of low fat dairy products results in further reductions in blood pressure (Appel *et al.*, 1997). Patients are prompted to find time to relax and reduce stress levels and to quit smoking. The inclusion of daily physical activity is highly recommended, as there is a large body of evidence to support the beneficial effects of exercise on resting blood pressure.

1.8 Exercise as a Treatment for Hypertension

1.8.1 Effects of Aerobic Exercise Training on Blood Pressure

A number of meta-analyses have examined the effects of aerobic exercise training on BP (Cornelissen and Fagard, 2005b; Dickinson *et al.*, 2006; Fagard and Cornelissen, 2007; Halbert *et al.*, 1997; Kelley and Kelley, 2001; Murphy *et al.*, 2007; Whelton *et al.*, 2002). Most meta-analyses found that endurance exercise decreases SBP 3-5 mm Hg, that it decreases DBP 2-3 mm Hg (Cornelissen and Fagard, 2005b; Dickinson *et al.*, 2006; Fagard and Cornelissen, 2007; Halbert *et al.*, 1997; Whelton *et al.*, 2002), and that these decreases were

independent of both exercise intensity and frequency. A meta-analysis of endurance exercise in older adults found only a 2 mm Hg decrease in SBP and a non-significant decrease in DBP of only 1 mm Hg (Kelley and Kelley, 2001). This may be due to the fact that few hypertensives were included in these trials and exercise training generally elicits greater BP reductions in hypertensives than in normotensives (Cornelissen and Fagard, 2005b). A meta-analysis of the effect of walking on BP found a non-significant decrease in SBP and only a 1.52 mm Hg reduction in DBP (Murphy *et al.*, 2007).

The mechanisms responsible for BP reduction with aerobic exercise training are not fully understood. Cornelissen and Fagard (2005b) suggested that modulation of ANS activity may be responsible for the decrease in BP. Their meta-analysis found that after aerobic exercise training, there was a decrease in systemic vascular resistance accompanied by a decrease in plasma norepinephrine and a decrease in plasma renin activity. There was also a decrease in resting HR, suggesting increased parasympathetic activity, and no change in night-time BP when there is little sympathetic nervous activity. These findings combined suggest that an improvement in the ANS may be responsible for the lower resting BP.

Examination of the effects of exercise on BRS has produced positive results. Participants who were subjected to long-term exercise training showed increased BRS compared with controls (Ueno and Moritani, 2003). Both young (Iwasaki *et al.*, 2003) and older (Okazaki *et al.*, 2005) adults have shown

improvements in cardiovagal BRS following long-term, moderate intensity endurance training. A dose-response relationship was apparent as both groups showed increases during the first six months, with no further increases in older adults (Okazaki *et al.*, 2005) and a return to baseline values at one year in young adults (Iwasaki *et al.*, 2003). Short-term endurance training proved effective in increasing cardiovagal BRS, while having no effects on sympathetic BRS (Cooke, *et al.*, 2002a). These studies suggest that moderate aerobic exercise is effective in augmenting BRS for the first six months, though longer training may not result in further improvements.

Studies investigating the effects of endurance training on BPV have been equivocal. Some researchers have reported BPV modulation following three months of moderate intensity endurance training (Izdebska *et al.*, 2004), while others have found no changes following one (Uusitalo *et al.*, 2002) or five years (Uusitalo *et al.*, 2004) of moderate intensity training. These discrepancies are likely explained by differences in pre-training resting blood pressure values. Izdebska and colleagues (2004) found that hypertensive subjects decreased the LF component of systolic BPV to the same level as that in normotensive individuals. This adjustment in the ANS was related to changes in resting SBP. Training protocols that did not result in modulation of BPV also failed to have an effect on BP values (Uusitalo *et al.*, 2002, 2004).

Further studies examining the effects of endurance training on the ANS have demonstrated that training causes an increase in resting HRV (Carter, J.B. *et*

al., 2003a, 2003b; Madden *et al.*, 2006). This effect was noted in a variety of age groups, ranging from 19 (Carter, J.B. *et al.*, 2003b) to greater than 70 years of age (Madden *et al.*, 2006). There appears to be a dose-response relationship as progressive increases in intensity and duration are accompanied by increases in HRV (Okazaki *et al.*, 2005). However, there may be a threshold above which no further advantages are achieved and perhaps a decline in HRV is acquired (Iellamo *et al.*, 2002). A strong body of evidence supports the hypothesis that endurance training decreases BP and improves the ANS. Therefore, it is possible that modulation of the ANS is responsible for attenuating resting BP.

1.8.2 Effects of Resistance Exercise Training on Blood Pressure

Although there is a smaller body of evidence, resistance training has proved to be effective in lowering SBP by 3-5 mm Hg, and DBP by 3-4 mm Hg (Cornelissen and Fagard, 2005a; Kelley, 1997; Kelley and Kelley, 2000).

Mechanisms for BP reductions via resistance training have not been fully elucidated, but it appears that modulation of the ANS is not the cause. Only a few studies have examined the effects of resistance training on cardiovascular autonomic function, and evidence of training adaptations of the ANS is equivocal with some researchers reporting no effects (Forte *et al.*, 2003; Madden *et al.*, 2006; Van Hoof *et al.*, 1996), while others report increased HRV (Loimaala *et al.*, 2003; Selig *et al.*, 2004) following training. The discrepancy may be a result of differences in training protocols, as both of the studies reporting increased HRV

involved aerobic training in conjunction with resistance training, although one did attempt to utilise only small amount of leg and arm ergometry to minimise the effects of endurance exercise (Selig *et al.*, 2004).

Studies reporting other variables further support the hypothesis that resistance training does not elicit changes in sympathetic activity. Strength training did not cause decreases in resting heart rate (Carter, J.R. *et al.*, 2003; Cornelissen and Fagard, 2005a), nor did training have any affects on MSNA (Carter, J.R., *et al.*, 2003). Furthermore, no changes in plasma epinephrine or norepinephrine have been demonstrated following strength training (Cornelissen and Fagard, 2005a).

Studies of the BRS response to resistance training have been sparse and equivocal. One study reported increased BRS following a combination of endurance and strength training (Loimaala *et al.*, 2003). However, training consisting strictly of resistance exercise had no effect on cardiovagal BRS (Cooke and Carter, 2005). These authors did however suggest that although the training protocol did not affect the sensitivity of the baroreflex, it may have had an influence on "resetting" the baroreflex to a lower operating point, which would result in attenuated resting BP. Further research is necessary to determine the mechanisms underlying this phenomenon.

1.8.3 Effects of Isometric Exercise Training on Blood Pressure

An early examination of the effects of whole body isometric training on blood pressure found that thirty-two sessions lowered both SBP and DBP in hypertensive, but not normotensive participants (Kiveloff and Huber, 1971). Buck and Donner's (1985) early epidemiological study showed that men with occupations involving moderate to heavy isometric work had a lower incidence of hypertension than those with less daily isometric activity. These studies were the first to suggest that isometric training may have positive effects on BP.

1.8.3.1 Isometric Handgrip Training

More recently, researchers have examined the effects of low to moderate intensity isometric handgrip training (IHG) as a means to reduce BP. Contractions have been performed at 30 to 50% MVC and held for 30 to 120 seconds. This technique appears to be an effective training modality as it has effectively lowered BP in healthy adults (McGowan *et al.*, 2007; Ray and Carrasco, 2000; Wiley *et al.*, 1992), and both non-medicated (Peters *et al.*, 2006), and medicated hypertensive older adults (McGowan *et al.*, 2006; Taylor *et al.*, 2003). Training has shown to be effective in a laboratory setting, but adherence to independent training has not been studied.

The mechanisms responsible for attenuating BP remain undetermined. In normotensive participants, flow-mediated dilation, an index of endothelial function, is not changed with eight weeks of IHG, despite significantly attenuated BP (McGowan *et al.*, 2007). However, the same training elicited improvements

in flow-mediated dilation in hypertensive participants, even though maximal dilation was unaffected (McGowan *et al.*, 2006). These results suggest that endothelial dependant dilation was improved without structural changes to the vasculature (McGowan *et al.*, 2006).

Modified autonomic control may play a role in BP modification. Although Ray and Carrasco (2000) found that five weeks of IHG was insufficient to elicit changes in MSNA, Taylor and researchers (2003) found a significant increase in HF area of both HRV and BPV. BPV analysis also revealed decreased LF area and improved sympathovagal balance (Taylor *et al.*, 2003). These findings suggest that ten weeks of IHG increases PNS function and reduces sympathetic activity. Discrepancies may be due to training length or intensity, as the ANS may require more than five weeks, or lower intensity contractions to show a training effect. Support for decreased sympathetic activity is further supported by Peters and coworkers (2006), who found that six weeks of IHG training lowered resting BP due to attenuation of reactive oxygen species (ROS) following training. In recent years, researchers have proposed that ROS may be important in the development and maintenance of hypertension because of their inhibitory effect on NO, which activates the SNS (Campese *et al.*, 2003). Therefore, the ability of IHG to lower ROS may result in reduced sympathetic activation, and therefore attenuated BP. Although modulation of autonomic activity appears to be a likely mechanism in the reduction of BP with IHG, results are far from conclusive and further studies are necessary for clarification.

1.9 Purpose and Hypotheses

The purpose of this study was to examine the effects of six weeks of independent isometric handgrip training on blood pressure and autonomic function by examining baroreceptor sensitivity and both systolic and diastolic blood pressure variability. Measurement of pulse wave velocity was completed to examine the relationship between baroreflex changes and arterial stiffness.

We hypothesised that six weeks of home based IHG would attenuate resting blood pressure and improve autonomic function, demonstrated by an increase in baroreceptor sensitivity and decrease in blood pressure variability, and that these changes would be accompanied by improvements in arterial compliance, demonstrated by decreases in pulse wave velocity.

2.0 METHODS

2.1 Participants

Fourteen men and women (6 males and 8 females) aged 53 ± 11.1 years (range: 32 to 70 years) who were recently diagnosed as hypertensive volunteered to participate in this study. Eight participants were randomized to the isometric handgrip training (IHG) group and the remaining six participants served as controls. Participant demographics are shown in Table 3.1 in section 3.

2.1.1 Inclusion and Exclusion Criteria

Participants were eligible for this study if their physician had told them that they had high BP. Participants who were either pre-hypertensive or hypertensive according to the most recent Joint National Committee guidelines (Joint National Committee, 2003) were included in the study.

Participants who were diabetic, smokers, medicated for hypertension and/or other cardiovascular conditions, receiving hormone replacement therapy or who had heart failure were excluded from this study due to the potential confounding effects of these conditions on BP.

2.2 Study Design

This study was a between subject, repeated measures design. Groups were stratified according to resting BP ($< 140, \geq 140$), sex and age ($< 50, \geq 50$). Both groups were given pamphlets with information about lowering BP through

lifestyle modifications, similar to directions that physicians give their patients regarding BP control. In addition to this, the training group was required to complete three sessions of IHG for each of six weeks.

2.3 Testing

All testing sessions were completed in a temperature and noise controlled room in the Exercise Metabolism Research Laboratory at the McMaster University Ivor Wynne Centre. Participants arrived at the laboratory having fasted for four hours and having abstained from caffeine and alcohol for twelve hours and vigorous exercise for 24 hours prior to each of twelve visits. All sessions were completed between 1200h and 1800h, and every attempt was made to keep testing times consistent for each participant. The Hamilton Health Sciences/Faculty of Health Sciences Research Ethics Board approved this study.

2.3.1 Blood Pressure Measurement

During each visit to the laboratory, BP was measured in the brachial artery using an automated oscillometric blood pressure cuff (Dinamap Pro 100 V2), with the cuff positioned on the left upper arm approximately 2.5 cm superior to the antecubital fossa. Four measurements were taken in the supine position following five minutes of rest and four measurements were taken in the seated position following an additional five minutes of rest. The participants were randomly assigned to the order in which to complete these measurements. The last three

measurements in each set were averaged to calculate BP in each position and these two values were averaged to determine the daily BP reading.

2.3.2 Pre-Intervention Visits

A familiarization period consisted of two sessions, in which informed consent was obtained and the participants were able to accommodate to the investigators, laboratory and testing methods to ensure that accurate measurements could be achieved. During this time, baseline body weight and height were measured, and participants were given logs so that physical activity and nutritional habits could be recorded and assessed. The activity logs were provided throughout the study and completed weekly.

The third visit commenced with BP measurements followed by baseline testing for assessment of the autonomic nervous system as described below.

On the fourth visit BP readings were obtained. These were averaged with those of the second and third visit to determine baseline BP. From this value, participants were stratified into experimental and control groups based on SBP, sex and age. Participants in the experimental group were provided with a handgrip (Zona PLUS) and instructed on use. The first training session was completed in the laboratory under supervision to ensure proper use.

2.3.3 Visits during the intervention period

Over the next five weeks, participants reported to the laboratory once a week for BP measurements as described above. Participants in the experimental group completed one IHG training session at the laboratory under supervision following the first week of training to ensure proper use of the handgrip.

2.3.4 Post-intervention Visits

Immediately following the sixth week of the intervention period, participants reported to the laboratory to undergo post-intervention testing. This was preceded by BP measurements as described above. Body weight was measured and a diet log was provided for completion. Participants came to the laboratory twice more for BP measurements. The BP values from the final three visits were averaged to determine post-intervention BP.

2.3.5 Testing Procedure

Three electrodes were positioned on the chest for collection of lead II electrocardiograph (ECG) recordings (Cardiomatic MSC 7123). A finger photoplethysmograph (Finapres 2300, Ohmeda) was secured on the middle phalynx of the left middle finger for collection of beat-by-beat BP and a respiratory belt (Pneumotrace II, ADInsturments) was wrapped around the thorax at the level of the 6^{th} rib for collection of respiratory rate. All physiologic measures were sampled at 1000 Hz, input into a data acquisition board (PowerLab

ML795, ADInstruments) for analog-to-digital signal conversion with Chart5 software (ADInstruments) and stored on a personal computer (IBM Netvista) for offline analysis.

Participants were instructed to remain still and quiet for the duration of the testing protocol. After resting for five minutes on an electronic tilt table (Midland, 7208E) at 0°, continuous BP waveforms were collected for five minutes by manual applanation tonometry (Millar Instruments Inc, SPT-301) over the carotid artery, slightly inferior to the carotid sinus. After 20 additional minutes of supine rest, the participants were tilted to 40°. Participants remained in this position for ten minutes and were then tilted to 60° for an additional 15 minutes. Applanation tonometry of the carotid artery was repeated during the final five minutes of the 60° tilt. Participants were instructed to hold their left hand over their chest at heart level for the duration of the tilts.

2.4 Training Intervention

Participants were instructed to complete IHG in the seated position with feet resting on the floor. The training protocol is shown in figure 2.1. The IHG protocol began with the determination of the maximal voluntary contraction (MVC) of each hand with the dynamometer. Following a short rest period, four two-minute isometric contractions were sustained at 30% MVC using alternate hands. The handgrip device provided both visual and auditory feedback to ensure that the contraction was held at the proper intensity. Contractions were separated

by one-minute rest periods during which gentle stretching of the fingers and hands was recommended.

Upon completion of each training session, a score was assigned to give an index of how accurately the participant was able to maintain the contraction with 100 being a perfect score. Participants recorded their MVC and final score values following each session. Two IHG sessions were supervised in the laboratory, and the rest were completed independently. An exercise log was provided for tracking progress and adherence.

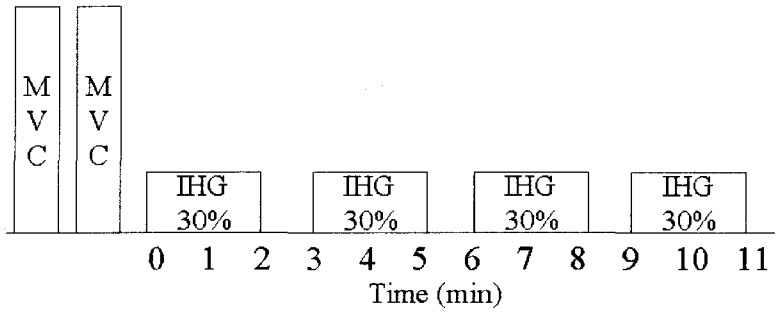

Figure 2.1: Isometric handgrip training protocol

2.5 Data Analysis

Raw data files from Chart5 were converted to text files. The data recorded during supine rest and 60° tilt both pre- and post-intervention for each participant were run with MATLAB software for analysis of baroreceptor sensitivity (BRS) and blood pressure variability (BPV). One participant was excluded from the control group due to poor quality data.

2.5.1 Analysis of Baroreceptor Sensitivity

Continuous recordings of RRI, and SBP were analysed for BRS using the sequence method (Kardos *et al.*, 2001). To determine BRS, the time series for RRI, SBP and DBP were scanned for sequences in which both RRI and either SBP or DBP concurrently increased or decreased for a minimum of three consecutive beats. A minimum of 1 mm Hg change in BP was considered significant for analysis. BRS was computed as the ratio ΔRRI/ΔSBP (ms/mm Hg) during supine rest and 60° tilt. A best fit line using the least squares method was found for each sequence of simultaneously increasing or decreasing RRI and systolic or diastolic BP. The computed values of BRS were accepted if there was a correlation coefficient of 0.8 or greater between R-R intervals and BP values. The software was written in MATLAB and has been validated previously in our laboratory (Stuckey *et al.*, 2007).

These files were transferred into Microsoft Excel (Microsoft Office 2003) for further analysis. The natural logarithm of each BRS value was calculated. Averages were calculated for each BRS measure (rising (BRS-R), lowering (BRS-L)) in each tilt position. The exponential value of these averages was taken to be the BRS. Averages were also calculated for all BRS values (BRS-A).

2.5.2 Analysis of Blood Pressure Variability

Continuous ECG and BP recordings were analysed. The ECG recording was used to locate the R-wave for each QRS complex using a peak-detection

algorithm (Pan and Tompkins, 1985) and a continuous R-R interval series was formed. From the R-R interval series the corresponding systolic and diastolic pressures were determined. Both systolic and diastolic pressure time series were re-sampled at a rate of 2 Hz, using linear interpolation, to produce a uniformly sampled heart rate signal. The BP signal from each steady state recording was divided into 128-second segments

Each BP series consisting of either systolic or diastolic values was analyzed as follows: Successive 128-second data sets (256 data points) from the BP series were subjected to Blackman-Tukey (BT) algorithm (Kay and Marple, 1981) for estimation of the power spectra: The mean value of corresponding BP was computed for each 128-second segment of the data and subtracted. A cosine window was attached to 5% of the signal at each end of the signal to minimize spectral leakage. An autocorrelation function was computed in the time domain. Fourier transform of the tapered autocorrelation function was computed to be the power spectrum of the time domain signal. The LF and HF components of BPV were characterised after identification of the respective peaks in each of the power spectral plots and the associated area under curve (AUC) was computed by numerical integration of the curve. From these data, HF area, LF area and LF:HF area ratio were computed for each 128-second segment. Absolute power spectral values for area were expressed as mm $Hg^2(Hz)^{-1}$. The total area under the power spectral curve was used as the reference and percentage area subtended by the LF and HF components were determined from the total power. Thereafter,

successive data from the power spectra data were averaged and mean LF area, mean HF area, LF:HF ratio, % LF area, % HF area were obtained for supine and 60° tilt. The software was written in MATLAB language. Abnormal beats were interpolated with an interpolation algorithm (Malik and Camm, 1995). The software for the present study has been used in our laboratory previously (Ditor *et al.*, 2005).

2.5.3 Analysis of Pulse Wave Velocity

PWV was analysed using the ECG recording and the BP waveforms from the finger and carotid pulses. Transit times for the finger (TT_f) and carotid pulses (TT_c) were calculated as the time from the R-spike of the ECG recording to the foot of the respective BP waveform (Figure 2.2). The foot of the BP waveform is considered to be the time point at the end of diastole and beginning of systole, and was considered to be the highest point of the second derivative of the BP signal.

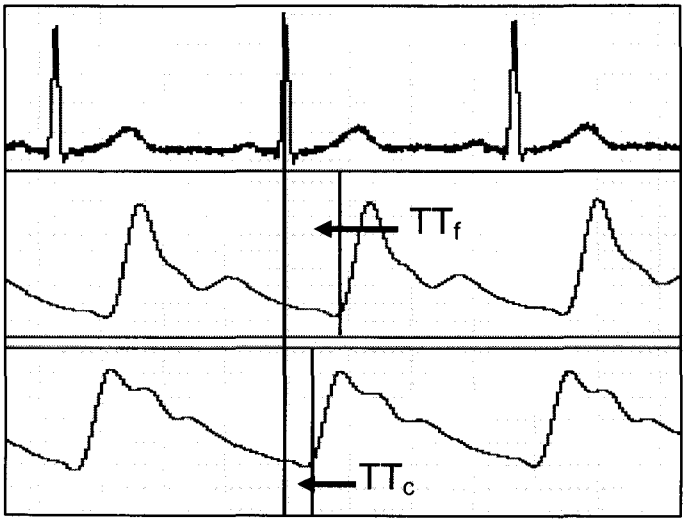

Figure 2.2: Determination of finger (TT_f) and carotid (TT_c) transit time.

Four or five sequences of fifteen consecutive beats were analysed and averaged for each participant in both supine and 60° tilt. PTT was calculated as the difference between TT_f and TT_c:

$$PTT = TT_f - TT_c \text{ (Equation 2.1).}$$

The distance (D) was calculated as the difference between the distance from the sternal notch to the second phalynx of the left middle finger (D_f) and the distance from the sternal notch to the left side of the neck at the level of the carotid artery just inferior to the carotid sinus (D_c):

$$D = D_f - D_c \text{ (Equation 2.2).}$$

PWV was the product of the distance and the inverse of PTT:

$$PWV = D(PTT)^{-1} \text{ (Equation 2.3).}$$

2.6 Statistical Analysis

Differences between intervention groups at baseline was analysed with a one way analysis of variance (ANOVA). Data that were not normal were analysed with an ANOVA on ranks. The pre- and post-intervention data were analysed using a two-factor (group x time) repeated measures ANOVA and a Tukey Honestly Significant Difference *post hoc* test was used to evaluate significant differences between the means (Sigma Stat 3.1, Systat Software Inc.). Pre- and post-intervention data that did not fit the assumptions of the ANOVA tests were analysed with Wilcoxon matched pairs tests for non-parametric data (Statistica 5.1, Statsoft Inc.). The relationship between PWV and BRS was

examined with linear regression (GraphPad Prism 4.01, GraphPad Software, Inc.). An alpha level of <0.05 was considered to be statistically significant. All results are presented as mean ± standard error of the mean (SEM).

3.0 Results

3.1 Participant Characteristics

There were no significant differences between the experimental and control group for systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), age, weight or height. Participant characteristics are shown in Table 3.1, and haemodynamic variables are shown in Table 3.2.

Table 3.1 Participant characteristics.

	Experimental	Control
Number of Participants	8	5
Number of Females	5	4
Number of Males	3	1
Age (years)	52.1 ± 4.0	54.4 ± 3.4
Weight (Kg)	73.6 ± 4.7	75.1 ± 4.6
Height (cm)	171.2 ± 3.2	164.5 ± 3.8

3.2 Pre-Intervention

Prior to the intervention period, there were no significant differences between the experimental and control groups for any baroreceptor sensitivity (BRS), diastolic blood pressure variability (DBPV) or pulse wave velocity (PWV) values in the supine state. No systolic blood pressure variability (SBPV) values differed between experimental and control groups except for the SBPV low frequency to high frequency ratio (LF:HF), which was higher in the experimental group ($p = 0.043$). There were no differences between any BRS, SBPV, DBPV or PWV values during pre-intervention testing during the 60° tilt.

There were no differences between groups for amount of physical activity, diet, or stress levels. These variables did not change for either group over the course of the study, but there was a trend toward increasing physical activity from pre- to post-intervention for both groups ($p = 0.073$).

3.3 Haemodynamics

There were no significant changes for any BP variables over the course of the study (Table 3.2; Figure 3.1, 3.2, 3.3). HR showed a trend toward a reduction over time as both the IHG and control groups showed a tendency to decrease HR over the course of the intervention ($p = 0.065$) (Table 3.2; Figure 3.4).

Table 3.2 Haemodynamic changes from pre- to post-intervention in the experimental and control groups.

	Experimental		Control	
	PRE	POST	PRE	POST
SBP (mm Hg)	140 ± 4.3	141 ± 3.7	135 ± 3.2	132 ± 5.2
DBP (mm Hg)	82 ± 2.8	85 ± 3.0	83 ± 4.2	82 ± 5.2
MAP (mm Hg)	102 ± 2.4	103 ± 2.7	101 ± 3.7	98 ± 5.2
HR (bpm)	66 ± 4.0	65 ± 3.7	73 ± 2.5	71 ± 2.2

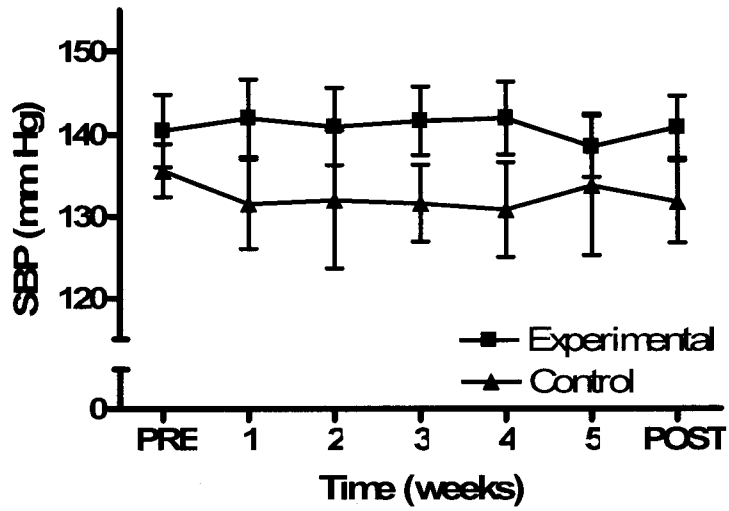

Figure 3.1: Weekly averages of systolic blood pressure for experimental and control groups.

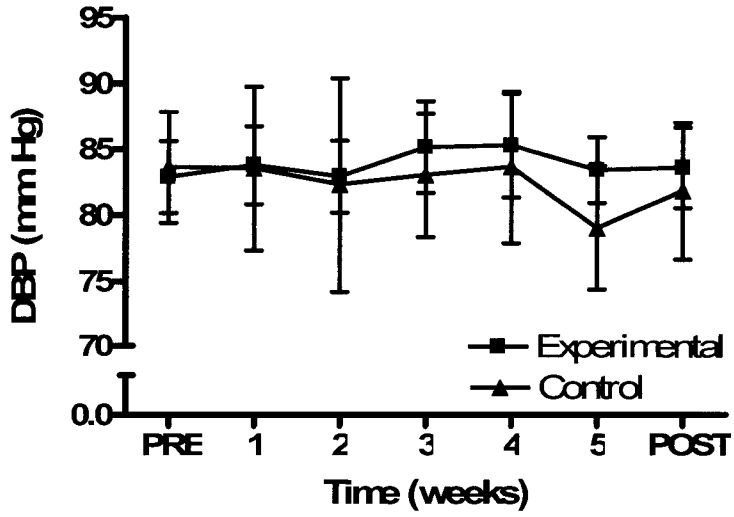

Figure 3.2: Weekly averages of diastolic blood pressure for experimental and control groups.

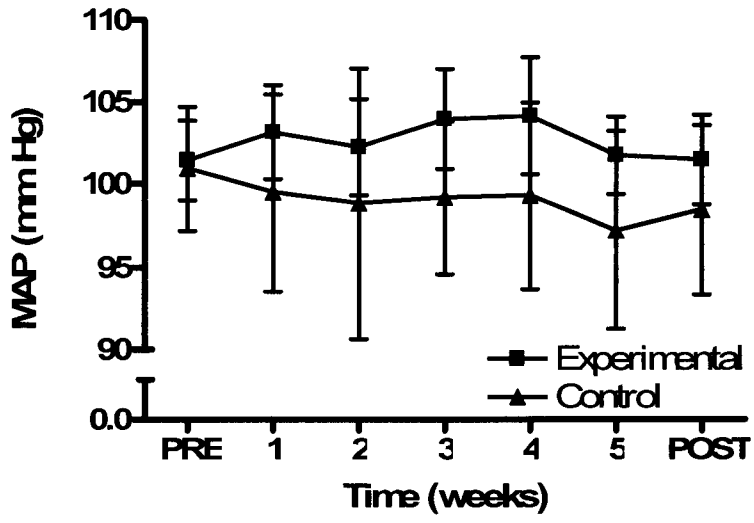

Figure 3.3: Weekly averages of mean arterial pressure for experimental and control groups.

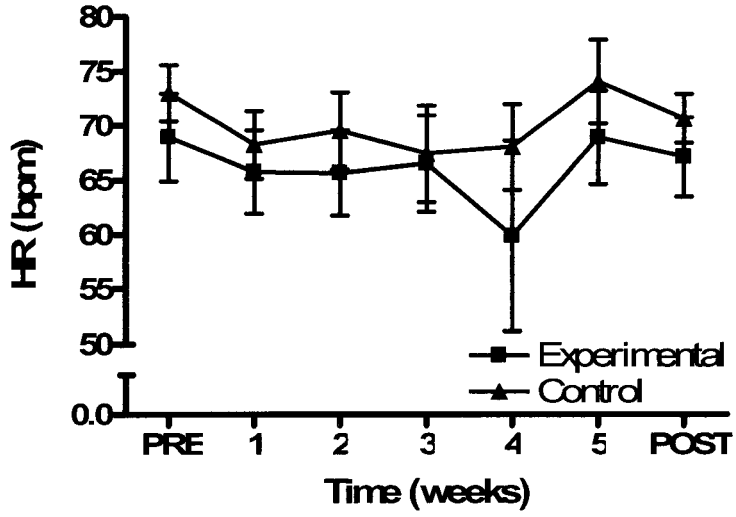

Figure 3.4: Weekly averages of heart rate for experimental and control groups.

3.4 Autonomic Changes

3.4.1 Baroreceptor Sensitivity

Supine BRS rising (BRS-R) and all BRS values (BRS-A) showed a significant decrease over time ($p = 0.02$; $p = 0.019$), while there was no change in BRS lowering (BRS-L) (Table 3.3; Figure 3.5). There were no significant changes for any BRS variable during the 60° tilt (Table 3.3; Figure 3.6).

Table 3.3 Changes in baroreceptor sensitivity from pre- to post-intervention in the experimental and control groups. All values are shown in Δms / Δmm Hg. * = significantly different from PRE ($p < 0.05$).

	Experimental		Control	
	PRE	POST	PRE	POST
Supine				
BRS-R	9.950 ± 2.253	*8.196 ± 1.660	8.300 ± 2.147	*7.119 ± 1.297
BRS-L	11.601 ± 2.644	11.401 ± 3.125	9.062 ± 2.118	8.260 ± 3.498
BRS-A	10.740 ± 2.401	*9.661 ± 2.260	8.625 ± 2.131	*7.636 ± 1.477
60° Tilt				
BRS-R	2.930 ± 0.452	3.296 ± 0.485	3.474 ± 1.161	2.290 ± 0.409
BRS-L	3.642 ± 0.485	3.741 ± 0.569	4.697 ± 1.735	2.979 ± 0.758
BRS-A	3.265 ± 0.455	3.512 ± 0.607	3.979 ± 1.421	2.605 ± 0.543

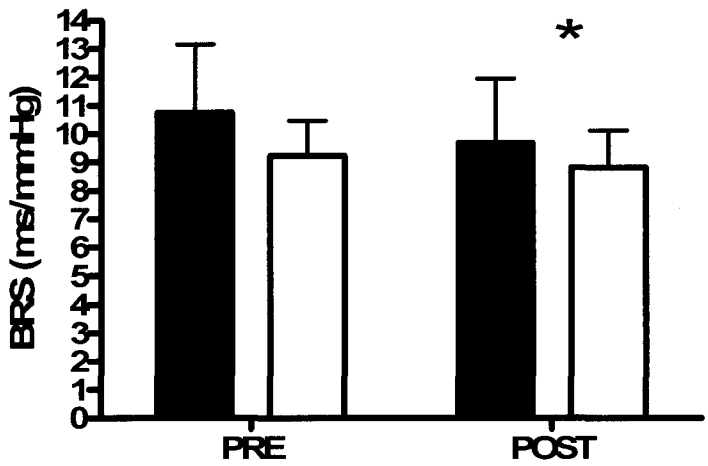

Figure 3.5: Pre- and Post-Intervention BRS-A values for experimental (black) and control (white) groups during supine rest.

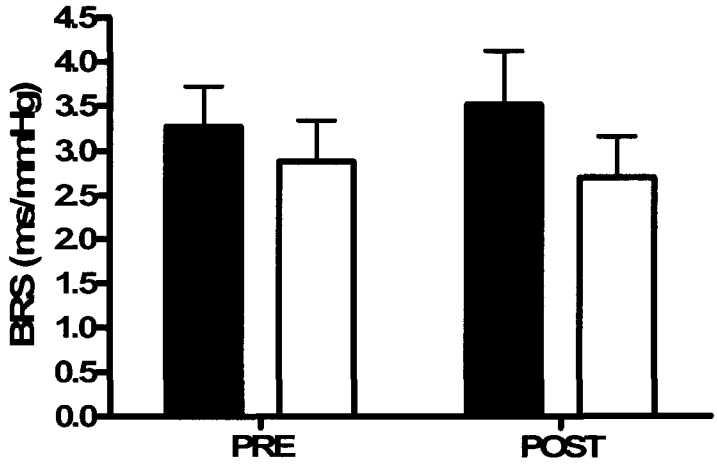

Figure 3.6: Pre- and Post-Intervention BRS-A values for experimental (black) and control (white) groups at a 60° tilt.

3.4.2 Systolic Blood Pressure Variability

For supine rest, there was a main effect for time for SBPV LF:HF ($p = 0.035$). There were no other significant changes, but SBPV HF showed a trend toward increasing after the intervention ($p = 0.093$). There were no significant changes for any SBPV variables during the 60° tilt. All SBPV values are shown in Table 3.4.

3.4.3 Diastolic Blood Pressure Variability

There were no significant changes for any DBPV variables either during supine rest or during the 60° tilt over the course of the intervention (Table 3.4).

Table 3.4 Systolic and diastolic blood pressure variability data pre- and post-intervention for experimental and control groups. LF and HF variables are expressed in (mm Hg)^{2}Hz^{-1}. * = significant main effect for time ($p < 0.05$).

	SBPV				DBPV			
	Experimental		Control		Experimental		Control	
	PRE	POST	PRE	POST	PRE	POST	PRE	POST
Supine								
LF	211.606 ± 8.929	192.624 ± 13.147	163.572 ± 21.618	161.731 ± 16.118	221.039 ± 6.328	217.217 ± 9.255	198.899 ± 12.770	209.358 ± 7.422
HF	42.387 ± 8.315	68.775 ± 12.308	88.805 ± 20.909	93.642 ± 16.268	32.130 ± 5.694	35.780 ± 8.758	53.071 ± 11.921	44.044 ± 7.284
LF:HF	6.787 ± 1.451	*4.598 ± 1.125	3.444 ± 1.941	*2.345 ± 0.890	8.510 ± 1.386	11.259 ± 2.144	5.647 ± 2.260	5.634 ± 1.408
%LF	83.255 ± 3.333	75.809 ± 5.081	64.720 ± 8.356	63.770 ± 6.184	87.269 ± 2.296	85.810 ± 3.506	78.874 ± 4.775	82.613 ± 2.870
%HF	16.745 ± 3.333	24.191 ± 5.081	35.280 ± 8.356	36.230 ± 6.184	12.731 ± 2.295	14.190 ± 3.506	21.126 ± 4.774	17.387 ± 2.870
60° Tilt								
LF	197.081 ± 17.396	188.325 ± 20.682	183.179 ± 22.931	168.196 ± 30.612	217.317 ± 15.931	213.773 ± 18.926	221.779 ± 3.712	205.693 ± 13.281
HF	57.308 ± 17.391	65.988 ± 20.610	69.853 ± 22.555	87.148 ± 30.530	37.466 ± 15.897	40.915 ± 18.940	30.331 ± 2.459	46.599 ± 12.377
LF:HF	5.507 ± 1.237	4.998 ± 1.432	4.872 ± 1.943	3.587 ± 1.259	11.878 ± 3.140	10.456 ± 2.332	7.556 ± 0.762	6.150 ± 1.693
%LF	77.471 ± 6.830	74.039 ± 8.103	72.342 ± 8.922	66.265 ± 11.999	85.354 ± 6.248	83.938 ± 7.433	87.956 ± 1.003	81.463 ± 4.962
%HF	22.528 ± 6.830	25.961 ± 8.104	27.658 ± 8.922	33.735 ± 11.999	14.711 ± 6.240	16.062 ± 7.433	12.044 ± 1.003	18.537 ± 4.962

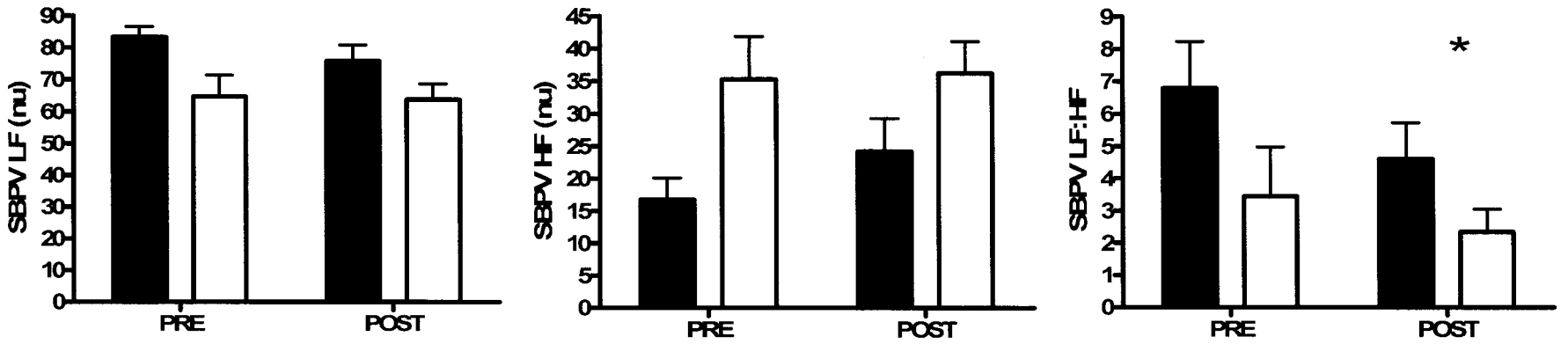

Figure 3.7: Systolic blood pressure variability Pre- and Post-intervention during supine rest in experimental (black) and control (white groups); percent Low Frequency (Left); percent High Frequency (Centre); Low Frequency-to-High Frequency ratio (Right).

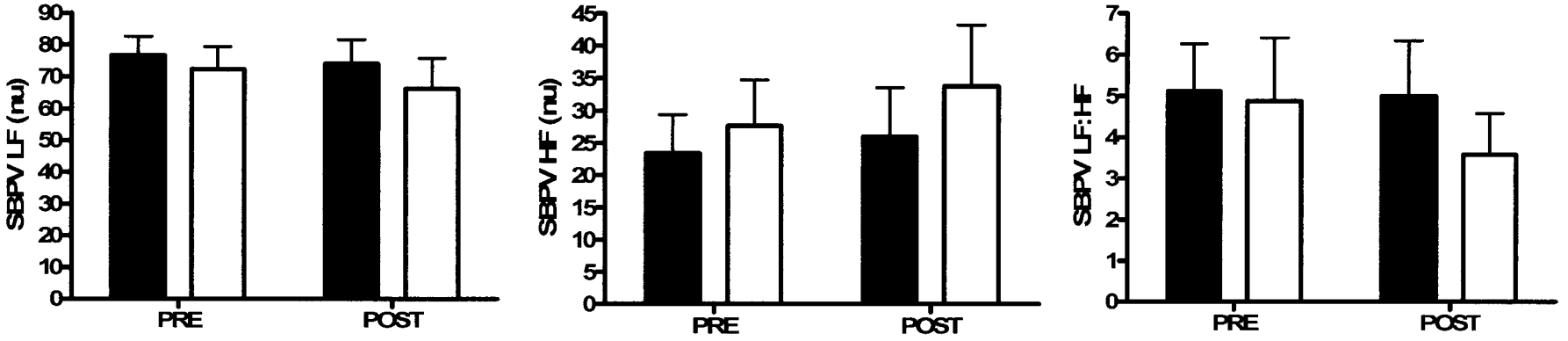

Figure 3.8: Systolic blood pressure variability Pre- and Post-intervention during a 60° tilt in experimental (black) and control (white groups); percent Low Frequency (Left); percent High Frequency (Centre); Low Frequency-to-High Frequency ratio (Right).

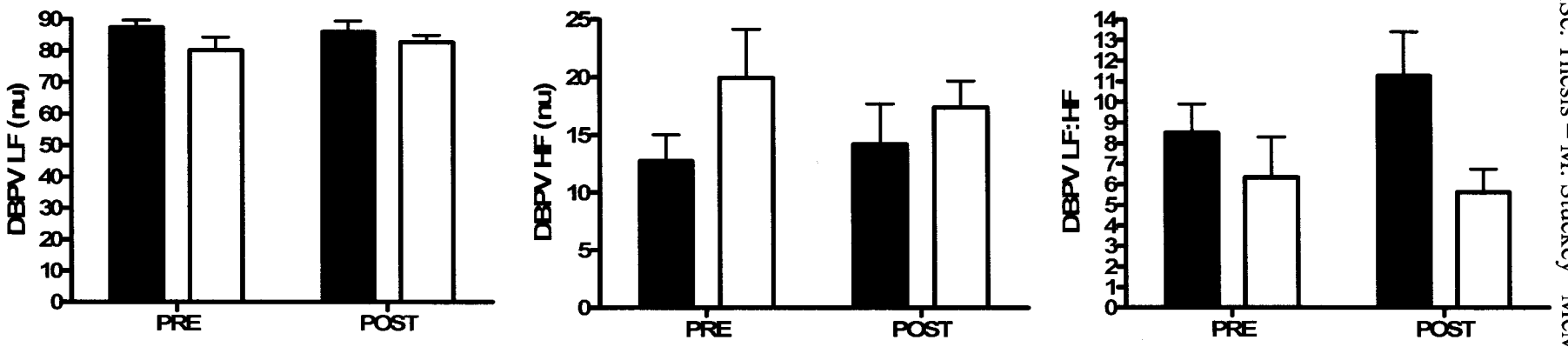

Figure 3.9: Diastolic blood pressure variability Pre- and Post-intervention during supine rest in experimental (black) and control (white groups); percent Low Frequency (Left); percent High Frequency (Centre); Low Frequency-to-High Frequency ratio (Right).

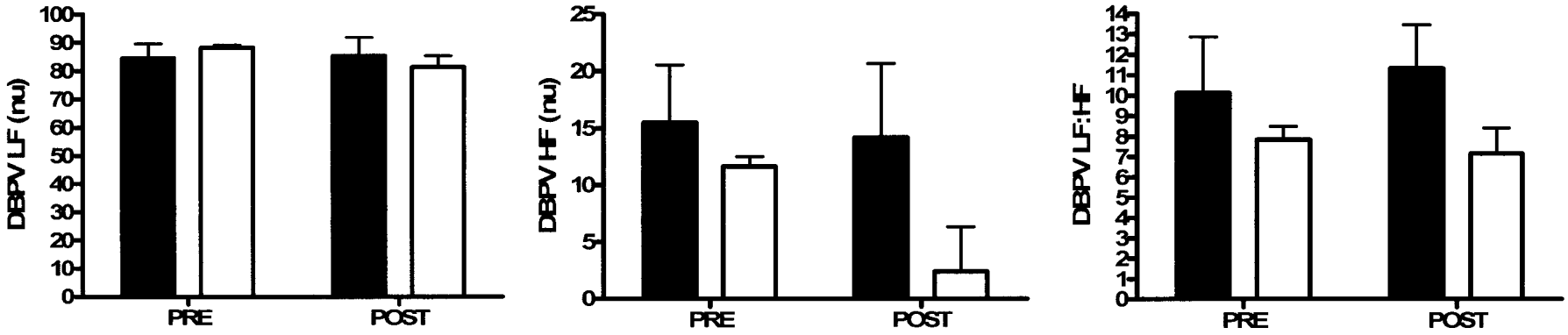

Figure 3.10: Diastolic blood pressure variability Pre- and Post-intervention during a 60° tilt in experimental (black) and control (white groups); percent Low Frequency (Left); percent High Frequency (Centre); Low Frequency-to-High Frequency ratio (Right).

3.5 Arterial Stiffness

There were no significant changes in PWV either supine or at 60° tilt. There was a significant positive relationship between BRS and PWV in the supine state ($p = 0.0026$) (Figure 3.11), but this relationship did not exist in the 60° tilt.

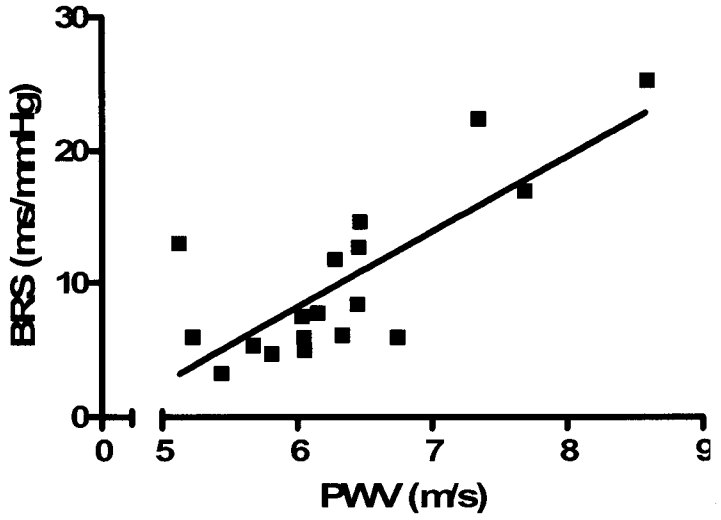

Figure 3.11: The relationship between BRS-A and PWV during supine rest ($r^2 = 0.61$; $p < 0.001$).

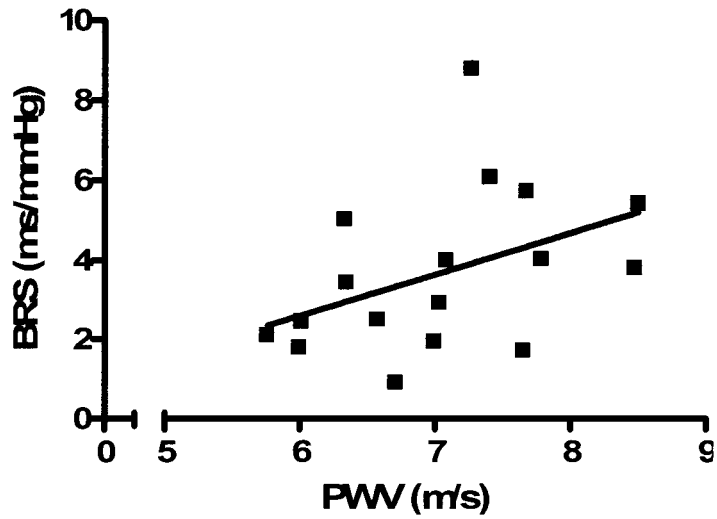

Figure 3.12: The relationship between BRS-A and PWV during 60° tilt ($r^2 = 0.19$; $p = 0.068$).

4.0 Discussion

4.1 Haemodynamic Measures

4.1.1 Blood Pressure

The main finding of this study is that six weeks of independent isometric handgrip training (IHG) in newly diagnosed hypertensives did not result in decreases in either systolic or diastolic blood pressure (SBP or DBP). This finding is not in accordance with other studies all of which report significant decreases in at least one BP variable (McGowan *et al.*, 2007; Peters *et al.*, 2006; Ray and Carrasco, 2000; Taylor *et al.*, 2003; Wiley *et al.*, 1992). However, in all of the above studies, most IHG sessions were supervised, ensuring that the majority of sessions were completed correctly. This study was novel in that participants were given an initial training session, supervised for one other and the remainder of the sessions were completed at home with self-reported completion and results. It is possible that either the reported 100% adherence was inaccurate or that the quality of unsupervised training was sub-optimal.

The present study may have failed to elicit significant findings due to the length of the intervention period. Other studies in which participants have trained for six weeks or less have either had the participants hold the isometric contractions at 50%MVC for 45 seconds (Peters *et al.*, 2006; Wiley *et al.*, 1992) or hold 30% MVC contractions for three minutes (Ray and Carrasco, 2000). Some shorter studies have had participants train four times per week (Ray and Carrasco, 2000; Wiley *et al.*, 1992). This difference in training regimen may be

responsible for the lack of significant changes in BP in the present study. However, unpublished research from our lab has shown that participants undergoing supervised IHG have reduced BP after only four weeks. Perhaps a longer intervention period is necessary for unsupervised training as there may be a longer learning period before IHG sessions are completed correctly, or after the initial observed sessions, participants may perform IHG with sub-optimal technique.

Two participants in the experimental group reported considerable pain that began or worsened after pre-intervention testing. One reported increased pain from sciatica and the other suffered from severe hip pain from osteoarthritis. As pain has been associated with increases in BP (Chawla and Kochar, 1999), this could have clouded our results; however, not all studies have demonstrated this relationship (Shiri *et al.*, 2007). When these two participants were excluded from the analysis, the experimental group experienced a slight but non-significant decrease in SBP from 140 ± 5.03 mm Hg to 137 ± 3.49 mm Hg. This indicates that a longer intervention period may have allowed for significant decreases in BP in the IHG group in the absence of external confounding factors.

4.1.2 Heart Rate

There were no significant changes in HR in either the experimental or control group. This is in accordance with other investigations that have shown that IHG has no effects on HR (Ray and Carrasco, 2000; Taylor *et al.*, 2003;

Wiley *et al.*, 1992). The non-significant trend towards decreased HR in both groups was likely associated with the increase in physical activity that was encouraged in both groups as a lifestyle modification as aerobic exercise training is known to decrease resting HR.

4.2 Autonomic Measures

4.2.1 Baroreceptor Sensitivity

This study found that six weeks of IHG lowered cardiovagal BRS, a finding contrary to what we expected. Other researchers have shown that aerobic exercise training results in augmented BRS (Iwasaki *et al.*, 2003; Okazaki *et al.*, 2005; Ueno and Moritani, 2003) and that resistance training increases (Loimaala *et al.*, 2003) or does not change BRS (Cooke and Carter, 2005). The effects of IHG on BRS had not been studied previously. This does not support our hypothesis that decreases in BP were due to improvements in BRS. However, since the present IHG protocol failed to elicit changes in BP, BRS may have responded to training differently than if BP had decreased. Further research is necessary with a larger sample size to determine how BRS changes in response to attenuated BP.

4.2.2 Blood Pressure Variability

There was a significant decrease in SBPV LF:HF following the six-week intervention period. This is in line with the study by Taylor and colleagues

(2003), who found a significant decrease in SBPV LF:HF following ten weeks of IHG training. However, in the present study, changes occurred in both the experimental and control group suggesting that lifestyle alterations were responsible for SBPV modulation.

There were no other significant changes in either SBPV or DBPV values. Although this is not in accordance with other researchers (Taylor *et al.*, 2003) this is likely due to the fact that improvements in BPV with physical training are related to reductions in BP (Uusitalo *et al.*, 2002, 2004; Izdebska *et al.*, 2004). Thus, since the present study was insufficient to attenuate BP, improved BPV variables would not be expected. This may also be due to differences in the length of the intervention period. Ray and Carrasco (2000) found no changes in sympathetic activity after only five weeks of IHG. Therefore, it is possible that ANS modulation takes longer than six weeks.

4.3 Arterial Stiffness

Training did not elicit any significant changes in PWV. Studies have demonstrated that training induced changes in central PWV are associated with concomitant changes in BP (Monahan *et al.*, 2001). Since the present IHG protocol did not result in reduced BP, changes in PWV would not be expected.

The positive relationship between PWV and cardiovagal BRS was the reverse of the expected relationship. PWV is generally negatively related to BRS, indicating that decreased arterial stiffness is related to better cardiovagal reflex

control (Chesterton *et al.*, 2005; Everson *et al.*, 2005; Monahan *et al.*, 2001). These studies, however, reported central arterial stiffness while the current investigation examined peripheral arterial stiffness. A study examining the effects of swim training on upper limb PWV found that PWV in children was significantly elevated in the training group compared with the sedentary group, and that there were no differences in adults (Vinet *et al.*, 2005). This suggests that peripheral PWV is affected differently by training than central compliance. The positive relationship may also be due to a type two error, as there were three outliers that influenced this relationship. A greater sample size would have helped to normalize the data and account for the outliers.

4.4 Potential Mechanisms

Although the findings of this study were inconclusive, the mechanism most likely responsible for BP reduction in hypertensives following IHG is ANS modulation. This is based on previous literature in which ten weeks of IHG reduced LF and increased HF power of HRV and BPV and lowered SBPV LF:HF (Taylor *et al.*, 2003). Another study found no changes in MSNA following five weeks of IHG (Ray and Carrasco, 2000), but this could be due to the shorter training period or because the population in this study was normotensive and it appears that BP reduction is accompanied by different physiological changes in hypertensives compared to normotensives (McGowan *et al.*, 2006, 2007). IHG also decreases reactive oxygen species (ROS) (Peters *et al.*, 2006) which reduces

sympathetic activity by enhancing the NO pathway (Campese *et al.*, 2003), indicating that ANS modulation may be secondary to reductions in ROS. Future studies with larger sample sizes are necessary to confirm this hypothesis, to determine which autonomic indices are altered and to examine relationships between these indices and other physiological variables.

4.5 Limitations

A major limitation of this study was lack of power. Given time restraints, recruitment of more participants was not possible. To increase the number of participants completing IHG, we could have forgone the control group since a number of studies have demonstrated the efficacy of IHG to lower BP. However, the results support the decision to include a control group, since this study did not simply involve IHG, but the addition of such training to recommended lifestyle modifications. Indeed, without the control group, this study would have concluded that IHG improves sympathovagal balance even though this may have resulted from lifestyle modifications.

Since this study investigated the applicability of IHG as a BP treatment outside of a laboratory or physician's office, training logs were based upon self-reported completion of training, which may not have been completed truthfully. However, since the purpose of this study was to test the effectiveness of independent IHG, the accuracy of reported training is irrelevant. If participants are unwilling or unable to complete the training either with the frequency or

quality of exercise necessary to elicit changes in BP and ANS indices, then IHG will not be an effective treatment if prescribed for patients to complete in an unsupervised environment. This treatment modality is perhaps most practically applicable as an addition to a regular physical activity regimen (Taylor, *et al.*, 2003).

Although only two of our participants were pre-menopausal, phase of the menstrual cycle was not controlled for and this has been reported to affect autonomic activity in some (Hirshoren *et al.*, 2002) but not all studies (Minson *et al.*, 2000). Our six week training protocol ensured that female participants were in the opposite phase of their cycle at post-intervention testing.

4.6 Conclusions

In conclusion, unsupervised IHG in the present study was insufficient to reduce BP in newly diagnosed hypertensives. Lifestyle modifications may have attenuated BRS and improved sympathovagal balance as demonstrated by a decrease in the SBPV LF:HF. Further large studies are necessary to determine how IHG as a hypertension treatment can be implemented to effectively control BP on a population level.

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6.0 Appendices

Appendix A – Raw Data

Pre- and Post-intervention participant characteristics.

		Weight		Height		BMI		Physical Activity	
Participant	**Group**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**
1	E	89.5	88.9	1.905	1.905	24.7	24.5	135	110
4	E	66.0	68.0	1.625	1.640	25.0	25.3	225	225
5	E	66.2	65.3	1.670	1.664	23.7	23.5	180	120
7	E	93.0	93.7	1.778	1.772	29.4	29.9	300	260
8	E	56.0	55.1	1.689	1.683	19.6	19.5	240	260
11	E	66.7	68.0	1.613	1.626	26.2	25.7	150	420
12	E	68.0	66.8	1.689	1.702	23.8	23.4	150	180
13	E	83.0	83.7	1.727	1.708	27.8	28.0	135	285
3	C	71.4	74.5	1.550	1.555	29.7	31.0	0	120
9	C	85.3	83.5	1.588	1.581	33.8	33.1	280	360
10	C	70.1	66.5	1.746	1.746	23.0	21.8	180	150
14	C	86.2	81.7	1.613	1.626	33.1	31.4	120	180
15	C	62.6	62.1	1.734	1.715	20.8	21.0	140	248
AVG EXP		**73.6**	**73.7**	**1.712**	**1.713**	**25.0**	**25.0**	**189**	**233**
SEM		**4.7**	**4.7**	**0.033**	**0.032**	**1.0**	**1.1**	**60**	**100**
AVG CTL		**75.1**	**73.6**	**1.646**	**1.645**	**28.1**	**27.7**	**144**	**212**
SEM		**4.6**	**4.2**	**0.040**	**0.037**	**2.6**	**2.6**	**45**	**43**

Weight is presented in kilograms (kg), height is presented in metres (m), body mass index (BMI) is presented in kg/m^2, physical activity is presented in minutes per week.
SEM, standard error of the mean.

Pre- and Post-intervention nutrition analysis: macronutrients.

		Kilocalories		% Carbohydrate		% Protein		% Fat	
Participant	**Group**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**
1	E	1810.4	2067.5	17	16	44	53	39	33
4	E	1169.0	1236.0	20	24	51	41	30	36
5	E	1717.0	1377.9	16	20	37	43	45	36
7	E	1830.7	2033.4	21	22	43	33	21	20
8	E	1695.5	2220.5	15	13	52	54	34	29
11	E	1374.7	1423.1	15	18	60	55	29	30
12	E	1622.3	1626.3	15	18	46	48	41	37
3	C	1128.6	1234.3	13	22	49	39	39	42
9	C	1335.2	1105.6	23	23	41	49	35	31
10	C	2134.3	1592.3	14	13	61	62	26	29
14	C	1835.2	1339.7	15	19	69	63	20	23
15	C	1752.3	1932.7	12	19	58	45	25	33
AVG EXP		**1602.8**	**1712.1**	**17.0**	**18.7**	**47.6**	**46.7**	**34.1**	**31.6**
SEM		**92.2**	**147.8**	**1.0**	**1.4**	**2.8**	**3.1**	**3.1**	**2.3**
AVG CTL		**1637.1**	**1440.9**	**15.4**	**19.2**	**55.6**	**51.6**	**29.0**	**31.6**
SEM		**180.2**	**146.6**	**2.0**	**1.7**	**4.9**	**4.7**	**3.5**	**3.1**

SEM, standard error of the mean.

Pre- and Post-intervention nutrition analysis: nutrients that affect blood pressure

		Sodium		Fibre		Caffeine		Alcohol	
Participant	**Group**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**
1	E	1441.4	3090.4	18.5	25.7	137.5	176.9	5.5	0.0
4	E	1582.7	2031.7	14.2	10.6	137.5	0.0	0.0	0.0
5	E	2770.9	1295.1	19.1	15.3	48.9	3.1	11.0	5.5
7	E	1366.4	1414.8	5.9	8.8	50.0	0.0	39.6	75.7
8	E	2443.0	3479.6	22.8	22.8	152.0	199.0	4.3	19.1
11	E	1151.4	1181.0	22.3	24.2	92.9	77.0	0.0	0.0
12	E	3446.6	2265.2	9.5	16.0	151.9	137.4	0.0	0.0
3	C	1348.9	2445.3	10.3	14.6	82.8	248.5	0.0	0.0
9	C	1846.0	1193.1	11.9	14.5	135.8	118.5	3.5	0.0
10	C	2196.8	1899.9	28.0	19.8	16.6	47.4	6.4	0.0
14	C	2168.3	1641.9	43.3	34.2	0.0	0.0	1.8	0.0
15	C	2606.2	2982.2	26.1	20.5	183.3	66.7	17.1	12.8
AVG EXP		**2028.9**	**2108.2**	**16.0**	**17.6**	**110.1**	**84.8**	**8.6**	**14.3**
SEM		**326.8**	**340.8**	**2.4**	**2.5**	**17.4**	**32.9**	**5.4**	**10.6**
AVG CTL		**2033.2**	**2032.5**	**23.9**	**20.7**	**83.7**	**96.2**	**5.8**	**2.6**
SEM		**209.4**	**312.0**	**6.0**	**3.6**	**34.7**	**42.5**	**3.0**	**2.6**

Sodium and caffeine are presented in milligrams, fibre and alcohol are presented in grams.
SEM, standard error of the mean.

Pre- and Post-intervention blood pressure and heart rate values.

		SBP		DBP		MAP		HR	
Participant	**Group**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**
1	E	128	122	78	79	94	94	63	60
4	E	144	153	75	82	98	105	51	54
5	E	147	140	77	78	100	99	64	63
7	E	144	150	96	96	112	114	65	60
8	E	163	146	80	74	108	98	61	60
11	E	125	133	79	88	95	103	85	83
12	E	132	134	81	82	98	99	82	79
13	E	141	149	93	98	109	115	60	60
3	C	144	149	99	101	114	117	77	76
9	C	127	119	73	70	91	86	81	74
10	C	136	126	82	77	100	93	70	71
14	C	141	136	82	81	102	99	70	63
15	C	130	129	82	80	98	96	67	69
AVG EXP		140	141	82	85	102	103	66	65
SEM		4.3	3.7	2.8	3.0	2.4	2.7	4.0	3.7
AVG CTL		135	132	83	82	101	98	73	71
SEM		3.21	5.15	4.16	5.22	3.70	5.16	2.55	2.24

Systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) are presented in mm Hg.
Heart rate (HR) is presented in beats per minute (bpm).
SEM, standard error of the mean.

Weekly systolic blood pressure (SBP) values.

Participant	Group	PRE	Week 1	Week 2	Week 3	Week 4	Week 5	POST
1	E	128	125	126	123	122	122	122
4	E	144	161	160	150	150	149	153
5	E	147	153	150	142	132	142	140
7	E	144	151	145	152	152	144	150
8	E	163	144	143	153	156	146	146
11	E	125	124	124	130	134	125	133
12	E	132	135	129	133	138	134	134
13	E	141	143	151	150	152	147	149
3	C	144	150	160	146	149	155	149
9	C	127	124	120	123	118	109	119
10	C	136	125	121	124	123	131	126
14	C	141	N/A	N/A	140	140	140	136
15	C	130	127	127	125	124	N/A	129
AVG EXP		**140**	**142**	**141**	**142**	**142**	**139**	**141**
SEM		**4**	**5**	**5**	**4**	**4**	**4**	**4**
AVG CTL		**136**	**132**	**132**	**132**	**131**	**134**	**132**
SEM		**3**	**6**	**8**	**5**	**6**	**9**	**5**

All values are presented in mm Hg.
SEM, standard error of the mean.

Weekly diastolic blood pressure (DBP) values.

Participant	Group	PRE	Week 1	Week 2	Week 3	Week 4	Week 5	POST
1	E	78	82	74	81	78	77	79
4	E	75	84	85	80	80	80	82
5	E	77	82	82	77	71	82	78
7	E	96	98	92	103	103	89	96
8	E	80	71	73	76	78	75	74
11	E	79	77	80	84	85	82	88
12	E	81	84	82	82	87	85	82
13	E	93	92	95	98	100	97	98
3	C	99	103	109	100	104	91	101
9	C	73	71	69	72	69	66	70
10	C	82	77	75	78	78	77	77
14	C	82	N/A	N/A	84	83	82	81
15	C	82	83	76	81	84	N/A	80
AVG EXP		**83**	**84**	**83**	**85**	**85**	**83**	**84**
SEM		**3**	**3**	**3**	**4**	**4**	**2**	**3**
AVG CTL		**84**	**84**	**82**	**83**	**84**	**79**	**82**
SEM		**4**	**6**	**8**	**5**	**6**	**5**	**5**

All values are presented in mm Hg.
SEM, standard error of the mean.

Weekly mean arterial pressure (MAP) values.

Participant	Group	PRE	Week 1	Week 2	Week 3	Week 4	Week 5	POST
1	E	95	96	91	95	93	92	93
4	E	98	110	110	103	103	103	106
5	E	100	106	105	99	91	102	99
7	E	112	116	110	119	119	107	114
8	E	108	95	96	102	104	99	98
11	E	94	93	95	99	101	96	103
12	E	98	101	98	99	104	101	99
13	E	109	109	114	115	117	114	115
3	C	114	119	126	115	119	112	117
9	C	91	89	86	89	85	80	86
10	C	100	93	90	93	93	95	93
14	C	102	N/A	N/A	103	102	101	99
15	C	98	98	93	96	97	N/A	96
AVG EXP		**101**	**103**	**102**	**104**	**104**	**102**	**101**
SEM		**2**	**3**	**3**	**3**	**4**	**2**	**3**
AVG CTL		**101**	**100**	**99**	**99**	**99**	**97**	**98**
SEM		**4**	**6**	**8**	**5**	**6**	**6**	**5**

All values are presented in mm Hg.
SEM, standard error of the mean.

Weekly heart rate (HR) values.

Participant	Group	PRE	Week 1	Week 2	Week 3	Week 4	Week 5	POST
1	E	63	62	58	54	61	60	60
4	E	51	54	55	57	61	57	54
5	E	64	66	63	67	71	64	63
7	E	65	61	62	65	65	65	60
8	E	61	60	59	60	60	73	60
11	E	85	86	87	93	97	94	83
12	E	82	78	78	75	8	77	79
13	E	60	59	63	61	56	61	60
3	C	77	73	77	79	80	86	76
9	C	81	72	75	75	72	74	74
10	C	70	70	66	63	65	66	71
14	C	70	N/A	N/A	66	67	70	63
15	C	67	58	60	54	56	N/A	69
AVG EXP		**69**	**66**	**66**	**67**	**60**	**69**	**67**
SEM		**4**	**4**	**4**	**4**	**9**	**4**	**4**
AVG CTL		**73**	**68**	**70**	**67**	**68**	**74**	**71**
SEM		**3**	**3**	**4**	**4**	**4**	**4**	**2**

All values are presented in beats per minute (bpm).
SEM, standard error of the mean.

Pre- and Post-intervention supine baroreceptor sensitivity values.

		BRS-R		BRS-L		BRS-A	
Participant	**Group**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**
1	E	24.3	17.8	26.1	27.7	25.2	22.4
4	E	7.6	5.7	7.3	5.9	7.4	5.8
5	E	5.9	5.2	5.8	5.2	5.9	5.2
7	E	8.7	7.7	9.4	8.8	9.0	8.3
8	E	10.5	8.9	19.0	22.2	14.5	14.9
11	E	12.3	11.6	13.4	11.9	12.9	11.7
12	E	5.4	5.3	6.7	6.3	6.0	5.8
13	E	4.7	3.0	5.2	3.3	4.9	3.2
3	C	3.9	3.7	5.4	5.1	4.6	4.4
9	C	7.3	8.3	8.0	9.8	7.7	9.1
10	C	16.5	11.9	17.3	13.3	16.9	12.6
14	C	6.4	5.9	8.2	8.3	7.2	6.9
15	C	7.5	5.8	6.4	4.9	6.8	5.3
AVG EXP		**9.9**	**8.2**	**11.6**	**11.4**	**10.7**	**9.7**
SEM		**2.3**	**1.7**	**2.6**	**3.1**	**2.4**	**2.3**
AVG CTL		**8.3**	**7.1**	**9.1**	**8.3**	**8.6**	**7.6**
SEM		**2.1**	**1.4**	**2.1**	**1.6**	**2.1**	**1.5**

All data are presented in ms/mm Hg.
BRS-R, rising baroreceptor sensitivity; BRS-L, lowering baroreceptor sensitivity; BRS-A, all baroreceptor sensitivity values.
SEM, standard error of the mean.

Pre- and Post-intervention 60° tilt baroreceptor sensitivity values.

		BRS-R		BRS-L		BRS-A	
Participant	**Group**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**
1	E	3.6	5.5	4.6	5.3	4.0	5.4
4	E	3.7	2.6	3.2	3.2	3.4	2.9
5	E	1.6	1.5	2.7	2.1	2.1	1.8
7	E	5.1	5.8	6.3	6.3	5.7	6.1
8	E	1.8	2.7	2.1	2.8	1.9	2.8
11	E	3.8	4.9	4.2	5.1	4.0	5.0
12	E	1.6	1.2	3.6	2.2	2.5	1.7
13	E	2.4	2.1	2.5	2.9	2.4	2.4
3	C	0.9	1.3	0.9	1.5	0.9	1.4
9	C	1.1	2.3	2.0	3.4	1.4	2.8
10	C	7.1	2.8	10.9	5.0	8.8	3.8
14	C	3.6	3.5	4.4	4.0	3.9	3.7
15	C	4.7	1.5	5.3	1.0	5.0	1.3
AVG EXP		**2.9**	**3.3**	**3.6**	**3.7**	**3.3**	**3.5**
SEM		**0.5**	**0.6**	**0.5**	**0.6**	**0.5**	**0.6**
AVG CTL		**3.5**	**2.3**	**4.7**	**3.0**	**4.0**	**2.6**
SEM		**1.2**	**0.4**	**1.7**	**0.8**	**1.4**	**0.5**

All data are presented in ms/mm Hg.
BRS-R, rising baroreceptor sensitivity; BRS-L, lowering baroreceptor sensitivity; BRS-A, all baroreceptor sensitivity values.
SEM, standard error of the mean.

Pre- and Post-intervention supine systolic blood pressure variability values

		LF		HF		LF:HF		%LF		%HF	
Participant	**Group**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**
1	E	216.2	221.5	38.8	32.9	5.6	6.7	84.8	87.1	15.2	12.9
4	E	234.4	224.1	20.3	90.0	11.5	7.5	92.0	88.2	8.0	11.8
5	E	225.7	192.7	29.4	62.1	7.7	3.1	88.5	75.6	11.5	24.4
7	E	179.7	201.2	71.1	52.8	2.5	3.8	71.7	79.2	28.3	20.8
8	E	238.0	232.1	17.5	23.0	13.6	10.1	93.2	91.0	6.8	9.0
11	E	223.0	191.5	32.2	63.4	6.9	3.0	87.4	75.1	12.6	24.9
12	E	207.5	154.0	46.9	99.0	4.4	1.6	81.6	60.9	18.4	39.1
13	E	168.4	123.9	82.9	127.1	2.0	1.0	67.0	49.4	33.0	50.6
3	C	98.9	139.6	151.7	122.3	0.7	1.2	39.5	55.4	60.5	44.6
9	C	157.6	177.7	95.6	77.4	1.6	2.3	62.2	69.7	37.8	30.3
10	C	156.5	143.6	96.6	108.3	1.6	1.3	61.8	57.0	38.2	43.0
14	C	170.4	130.1	79.1	122.7	2.2	1.1	68.3	51.5	31.7	48.5
15	C	234.5	217.6	21.0	37.5	11.1	5.8	91.8	85.3	8.2	14.7
AVG EXP		**211.6**	**192.6**	**42.4**	**68.8**	**6.8**	**4.6**	**83.3**	**75.8**	**16.7**	**24.2**
SEM		**8.9**	**13.1**	**8.3**	**12.3**	**1.5**	**1.1**	**3.3**	**5.1**	**3.3**	**5.1**
AVG CTL		**163.6**	**161.7**	**88.8**	**93.6**	**3.4**	**2.3**	**64.7**	**63.8**	**35.3**	**36.2**
SEM		**21.6**	**16.1**	**20.9**	**16.3**	**1.9**	**0.9**	**8.4**	**6.2**	**8.4**	**6.2**

Low frequency (LF) and high frequency (HF) values are presented in $(mm\ hg)^2Hz^{-1}$. All other values are in normalized units.
SEM, Standard error of the mean.

Pre- and Post-intervention 60° tilt systolic blood pressure variability values

		LF		HF		LF:HF		%LF		%HF	
Participant	**Group**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**
1	E	207.9	220.2	46.4	34.9	4.5	6.3	81.8	86.3	18.2	13.7
4	E	224.0	224.0	30.0	30.0	7.5	7.5	88.2	88.2	11.8	11.8
5	E	226.4	197.4	28.6	56.7	7.9	3.5	88.8	77.7	11.2	22.3
7	E	229.5	235.0	24.4	20.2	9.4	11.6	90.4	92.1	9.6	7.9
8	E	162.2	164.1	91.1	88.9	1.8	1.8	64.0	64.9	36.0	35.1
11	E	107.1	75.9	147.8	178.6	0.7	0.4	42.0	29.8	58.0	70.2
12	E	222.4	201.6	32.9	52.5	6.8	3.8	87.1	79.3	12.9	20.7
13	E	164.2	204.2	87.4	47.6	1.9	4.3	65.3	81.1	34.7	18.9
3	C	227.7	210.5	26.5	44.1	8.6	4.8	89.6	82.7	10.4	17.3
9	C	107.8	59.3	145.5	191.1	0.7	0.3	42.6	23.7	57.4	76.3
10	C	183.0	224.4	67.5	30.8	2.7	7.3	73.0	87.9	27.0	12.1
14	C	233.2	142.6	22.4	122.2	10.4	1.3	91.2	55.9	8.8	44.1
15	C	207.9	220.2	46.4	34.9	4.5	6.3	81.8	86.3	18.2	13.7
AVG EXP		**197.1**	**188.3**	**57.3**	**66.0**	**5.5**	**5.0**	**77.5**	**74.0**	**22.5**	**26.0**
SEM		**17.4**	**20.7**	**17.4**	**20.6**	**1.2**	**1.4**	**6.8**	**8.1**	**6.8**	**8.1**
AVG CTL		**183.2**	**168.2**	**69.9**	**87.1**	**4.9**	**3.6**	**72.3**	**66.3**	**27.7**	**33.7**
SEM		**22.9**	**30.6**	**22.6**	**30.5**	**1.9**	**1.3**	**8.9**	**12.0**	**8.9**	**12.0**

Low frequency (LF) and high frequency (HF) values are presented in $(mm\ hg)^2 Hz^{-1}$. All other values are in normalized units.
SEM, Standard error of the mean.

Pre- and Post-intervention supine diastolic blood pressure variability values

		LF		HF		LF:HF		%LF		%HF	
Participant	**Group**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**
1	E	200.1	182.2	52.1	68.9	3.8	2.6	79.4	72.6	20.6	27.4
4	E	234.3	237.9	20.4	17.2	11.5	13.8	92.0	93.2	8.0	6.8
5	E	237.9	240.0	17.0	14.3	14.0	16.8	93.3	94.4	6.7	5.6
7	E	221.7	229.1	31.3	24.8	7.1	9.2	87.6	90.2	12.4	9.8
8	E	219.9	223.4	33.1	29.2	6.6	7.7	86.9	88.4	13.1	11.6
11	E	233.4	227.8	21.5	25.0	10.8	9.1	91.6	90.1	8.4	9.9
12	E	232.5	227.2	20.9	26.1	11.1	8.7	91.7	89.7	8.3	10.3
13	E	188.5	170.0	60.6	80.7	3.1	22.1	75.7	67.8	24.3	32.2
3	C	184.8	208.8	64.8	43.6	2.9	4.8	74.1	82.7	25.9	17.3
9	C	172.7	190.6	79.5	63.3	2.2	3.0	68.5	75.1	31.5	24.9
10	C	179.2	214.9	70.8	36.7	2.5	5.9	71.7	85.4	28.3	14.6
14	C	219.3	198.6	33.4	55.2	6.6	3.6	86.8	78.2	13.2	21.8
15	C	238.5	233.9	16.9	21.4	14.1	10.9	93.4	91.6	6.6	8.4
AVG EXP		**221.0**	**217.2**	**32.1**	**35.8**	**8.5**	**11.3**	**87.3**	**85.8**	**12.7**	**14.2**
SEM		**6.3**	**9.3**	**5.7**	**8.8**	**1.4**	**2.1**	**2.3**	**3.5**	**2.3**	**3.5**
AVG CTL		**198.9**	**209.4**	**53.1**	**44.0**	**5.6**	**5.6**	**78.9**	**82.6**	**21.1**	**17.4**
SEM		**12.8**	**7.4**	**11.9**	**7.3**	**2.3**	**1.4**	**4.8**	**2.9**	**4.8**	**2.9**

Low frequency (LF) and high frequency (HF) values are presented in $(mm\ hg)^2Hz^{-1}$. All other values are in normalized units.
SEM, Standard error of the mean.

Pre- and Post-intervention 60° tilt diastolic blood pressure variability values

		LF		HF		LF:HF		%LF		%HF	
Participant	**Group**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**	**PRE**	**POST**
1	E	218.5	240.4	35.8	14.6	6.1	16.4	85.9	94.3	14.1	5.7
4	E	227.1	234.9	26.7	19.5	8.5	12.1	89.9	92.3	10.5	7.7
5	E	243.4	242.2	11.7	12.4	20.8	19.5	95.4	95.1	4.6	4.9
7	E	236.1	236.4	18.9	18.9	12.5	12.5	92.6	92.6	7.4	7.4
8	E	219.5	224.8	35.2	29.4	6.2	7.6	86.2	88.4	13.8	11.6
11	E	133.5	112.2	121.2	142.6	1.1	0.8	52.4	44.0	47.6	56.0
12	E	244.2	232.1	11.0	22.7	22.2	10.2	95.7	91.1	4.3	8.9
13	E	219.3	225.4	34.2	27.4	6.4	8.2	86.5	89.1	13.5	10.9
3	C	228.7	223.1	25.4	31.4	9.0	7.1	90.0	87.7	10.0	12.3
9	C	211.5	173.3	32.1	70.8	6.6	2.4	86.8	71.0	13.2	29.0
10	C	217.7	233.1	36.3	21.5	6.0	10.9	85.7	91.6	14.3	8.4
14	C	231.7	173.6	23.7	81.9	9.8	2.1	90.7	67.9	9.3	32.1
15	C	218.5	240.4	35.8	14.6	6.1	16.4	85.9	94.3	14.1	5.7
AVG EXP		**217.3**	**213.8**	**37.5**	**40.9**	**11.9**	**10.5**	**85.4**	**83.9**	**14.7**	**16.1**
SEM		**15.9**	**18.9**	**15.9**	**18.9**	**3.1**	**2.3**	**6.2**	**7.4**	**6.2**	**7.4**
AVG CTL		**221.8**	**205.7**	**30.3**	**46.6**	**7.6**	**6.2**	**88.0**	**81.5**	**12.0**	**18.5**
SEM		**3.7**	**13.3**	**2.5**	**12.4**	**0.8**	**1.7**	**1.0**	**5.0**	**1.0**	**5.0**

Low frequency (LF) and high frequency (HF) values are presented in $(mm\ hg)^2 Hz^{-1}$. All other values are in normalized units.
SEM, Standard error of the mean.

Pre- and Post-intervention pulse wave velocity values.

		Peripheral PWV				Carotid PWV			
		Supine		60° Tilt		Supine		60° Tilt	
Participant	Group	PRE	POST	PRE	POST	POST	PRE	PRE	POST
1	E	8.598	7.350	7.789	8.503	0.877	0.833	0.751	0.692
4	E	6.042	6.055	6.347	7.030	1.348	1.271	1.138	1.080
5	E	5.231	N/A	5.761	6.000	0.687	N/A	0.867	0.848
7	E	N/A	6.449	7.678	7.407	N/A	1.321	0.883	0.961
8	E	6.469	6.652	N/A	N/A	1.189	1.238	N/A	N/A
11	E	N/A	6.284	7.084	6.335	N/A	1.022	0.607	0.957
12	E	6.339	6.750	N/A	7.654	1.207	1.164	N/A	1.046
13	E	6.060	5.446	6.014	6.014	1.155	1.363	1.058	0.997
3	C	5.817	N/A	6.709	N/A	1.097	N/A	0.865	N/A
9	C	6.156	N/A	N/A	N/A	1.224	N/A	N/A	N/A
10	C	7.692	6.460	7.268	8.474	0.839	0.830	0.723	0.667
14	C	5.770	6.457	N/A	N/A	1.247	1.276	N/A	N/A
15	C	7.727	6.856	7.723	7.182	1.127	1.015	0.805	0.786
AVG EXP		**6.456**	**6.427**	**6.779**	**6.992**	**1.077**	**1.173**	**0.884**	**0.940**
SEM		**0.463**	**0.225**	**0.353**	**0.354**	**0.100**	**0.071**	**0.079**	**0.050**
AVG CTL		**6.632**	**6.591**	**7.234**	**7.828**	**1.107**	**1.040**	**0.798**	**0.726**
SEM		**0.445**	**0.133**	**0.293**	**0.646**	**0.073**	**0.129**	**0.041**	**0.059**

All values are represented as m/s.
SEM, standard error of the mean.

Appendix B – Analysis of Variance Summary Tables

Diastolic Blood Pressure

Source of Variation	DF	SS	MS	F	P
Group	1	4.734	4.734	0.0300	0.866
Participant(Group)	11	1737.890	157.990		
Time	1	0.934	0.934	0.128	0.728
Group x Time	1	22.755	22.755	3.106	0.106
Residual	11	80.579	7.325		
Total	25	1850.471	74.019		

Baroreceptor Sensitivity Rising Supine

Source of Variation	DF	SS	MS	F	P
Group	1	15.397	15.397	0.306	0.591
Participant(Group)	11	553.338	50.303		
Time	**1**	**18.050**	**18.050**	**7.414**	**0.020**
Group x Time	1	0.0289	0.0289	0.0119	0.915
Residual	11	26.780	2.435		
Total	25	614.962	24.598		

Baroreceptor Sensitivity Lowering Supine

Source of Variation	DF	SS	MS	F	P
Group	1	49.638	49.638	0.516	0.487
Participant(Group)	11	1057.654	96.150		
Time	1	1.545	1.545	0.871	0.371
Group x Time	1	0.558	0.558	0.315	0.586
Residual	11	19.511	1.774		
Total	25	1128.572	45.143		

Systolic Blood Pressure Variability Low Frequency Area Supine

Source of Variation	DF	SS	MS	F	P
Group	1	9583.890	9583.890	4.340	0.061
Participant(Group)	11	24290.235	2208.203		
Time	1	667.118	667.118	1.669	0.223
Group x Time	1	452.038	452.038	1.131	0.310
Residual	11	4396.054	399.641		
Total	25	39719.997	1588.800		

Systolic Blood Pressure Variability High Frequency Area Supine

Source of Variation	DF	SS	MS	F	P
Group	1	7817.730	7817.730	3.999	0.071
Participant(Group)	11	21503.733	1954.885		
Time	1	1499.956	1499.956	3.375	0.093
Group x Time	1	714.552	714.552	1.608	0.231
Residual	11	4888.857	444.442		
Total	25	37054.093	1482.164		

Systolic Blood Pressure Variability Low Frequency-to-High Frequency Ratio Supine

Source of Variation	DF	SS	MS	F	P
Group	1	48.164	48.164	2.134	0.172
Participant(Group)	11	248.259	22.569		
Time	**1**	**16.639**	**16.639**	**5.769**	**0.035**
Group x Time	1	1.829	1.829	0.634	0.443
Residual	11	31.727	2.884		
Total	25	350.345	14.014		

Systolic Blood Pressure Variability % Low Frequency Supine

Source of Variation	DF	SS	MS	F	P
Group	1	1438.180	1438.180	4.449	0.059
Participant(Group)	11	3556.011	323.274		
Time	1	108.448	108.448	1.772	0.210
Group x Time	1	64.941	64.941	1.061	0.325
Residual	11	673.151	61.196		
Total	25	5891.396	235.656		

Systolic Blood Pressure Variability % High Frequency Supine

Source of Variation	DF	SS	MS	F	P
Group	1	1438.180	1438.180	4.449	0.059
Participant(Group)	11	3556.011	323.274		
Time	1	108.448	108.448	1.772	0.210
Group x Time	1	64.941	64.941	1.061	0.325
Residual	11	673.151	61.196		
Total	25	5891.396	235.656		

Pulse Wave Velocity Supine

Source of Variation	DF	SS	MS	F	P
Group	1	1.346	1.346	0.931	0.367
Participant(Group)	7	10.117	1.445		
Time	1	0.197	0.197	0.483	0.510
Group x Time	1	0.249	0.249	0.611	0.460
Residual	7	2.858	0.408		
Total	17	14.657	0.862		

Appendix C: Wilcoxon Summary Tables

Systolic Blood Pressure

	Valid N	T	Z	p-level
PRE & POST	13	43	0.174714	0.861305

Heart Rate

	Valid N	T	Z	p-level
PRE & POST	13	15.5	1.843492	0.065266

Baroreceptor Sensitivity All Supine

	Valid N	T	Z	p-level
PRE & POST	13	12	2.341169	**0.01923**

Baroreceptor Sensitivity Rising 60° Tilt

	Valid N	T	Z	p-level
PRE & POST	13	44	0.104828	0.916513

Baroreceptor Sensitivity Lowering 60° Tilt

	Valid N	T	Z	p-level
PRE & POST	13	45	0.034943	0.972126

Baroreceptor Sensitivity All 60° Tilt

	Valid N	T	Z	p-level
PRE & POST	13	43	0.174714	0.861305

Systolic Blood Pressure Variability – Low Frequency Area 60° Tilt

	Valid N	T	Z	p-level
PRE & POST	12	23	0.889108	0.373951

Systolic Blood Pressure Variability – High Frequency Area 60° Tilt

	Valid N	T	Z	p-level
PRE & POST	12	23	0.889108	0.373951

Systolic Blood Pressure Variability – Low Frequency-to-High Frequency Ratio 60° Tilt

	Valid N	T	Z	p-level
PRE & POST	12	26	0.622376	0.533699

Systolic Blood Pressure Variability – % Low Frequency 60° Tilt

	Valid N	T	Z	p-level
PRE & POST	12	23	0.889108	0.373951

Systolic Blood Pressure Variability – % High Frequency 60° Tilt

	Valid N	T	Z	p-level
PRE & POST	12	23	0.889108	0.373951

Diastolic Blood Pressure Variability – Low Frequency Area Supine

	Valid N	T	Z	p-level
PRE & POST	13	33	0.873571	0.382359

Diastolic Blood Pressure Variability – High Frequency Area Supine

	Valid N	T	Z	p-level
PRE & POST	13	45	0.034943	0.972126

Diastolic Blood Pressure Variability – Low Frequency-to-High Frequency Ratio Supine

	Valid N	T	Z	p-level
PRE & POST	13	36	0.663914	0.50675

Diastolic Blood Pressure Variability – % Low Frequency Supine

	Valid N	T	Z	p-level
PRE & POST	13	44	0.104828	0.916513

Diastolic Blood Pressure Variability – % High Frequency Supine

	Valid N	T	Z	p-level
PRE & POST	13	44	0.104828	0.916513

Diastolic Blood Pressure Variability – Low Frequency Area 60° Tilt

	Valid N	T	Z	p-level
PRE & POST	12	33	0.470679	0.637873

Diastolic Blood Pressure Variability – High Frequency Area 60° Tilt

	Valid N	T	Z	p-level
PRE & POST	12	32	0.549125	0.582923

Diastolic Blood Pressure Variability – Low Frequency-to-High Frequency Ratio 60° Tilt

	Valid N	T	Z	p-level
PRE & POST	12	37	0.156893	0.87533

Diastolic Blood Pressure Variability – % Low Frequency 60° Tilt

	Valid N	T	Z	p-level
PRE & POST	12	32	0.549125	0.582923

Diastolic Blood Pressure Variability – % High Frequency 60° Tilt

	Valid N	T	Z	p-level
PRE & POST	12	32	0.549125	0.582923

Pulse Wave Velocity 60° Tilt

	Valid N	T	Z	p-level
PRE & POST	9	14	1.006993	0.313946