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The effects of isometric handgrip exercise on post-exercise hypotension, ambulatory arterial blood pressure and heart rate variability in individuals medicated for hypertension

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Abstract

Isometric handgrip (IHG) training lowers resting blood pressure (BP) and improves heart rate variability (HRV) in hypertensives, yet neither the acute responses nor the effects of training on these responses are known. IHG training effects on 24-hr ambulatory BP have also yet to be examined. To address these voids, 11 hypertensive individuals (medicated) performed 4, 2-min IHG contractions at 30% MVC, 3x/wk for 8 wks, and 9 age-matched medicated hypertensives served as controls. At baseline, mid- and post-training, BP and HRV were assessed prior to and following acute IHG, with BP monitored for 22 hrs post-IHG. Resting and ambulatory BP were measured on a separate day. Acute nor chronic IHG exercise altered resting BP or HRV, and 24-hour ambulatory BP was unchanged with training (all P > 0.05). These findings suggest that IHG (acute and chronic) does not influence BP or HRV in our population of well-controlled medicated hypertensives.

Dedication

   I want to dedicate this to my family and friends. Thank you for supporting me throughout this project. To my mom and stepdad, Gabriele and David, thank you for always being there to chat and for allowing me to vent my frustrations. Thank you for always having a safe haven for me to escape to when things got too crazy or cold here. To my dad and stepmom, Bill and Betty, thank you for being supportive and always keeping me well nourished. Dad, these past two years have been great. Thank you for dealing with all my ups and downs along the way.

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Abbreviations:

ABP	- Arterial blood pressure
ACEI	- Angiotensin converting enzyme inhibitor
ACSM	- American College of Sports Medicine
ADP	- Adenosine diphosphate
AMP	- Adenosine monophosphate
ANS	- Autonomic nervous system
AR	- Autoregressive modeling
ARB	- Angiotensin receptor blocker
ATP	- Adenosine triphosphate
BB	- β blocker
cAMP	- Cyclic adenosine monophosphate
CC	- Central Command
CCC	- Cardiovascular control center
CGSA	- Course graining spectral analysis
CO	- Cardiac output
CVD	- Cardiovascular disease
DASH	- Dietary approaches to stop hypertension
DBP	- Diastolic blood pressure
FFT	- Fast Fourier transformation
HF	- High frequency
HR	- Heart rate
HRV	- Heart rate variability
HT	- Hypertension
IHG	- Isometric handgrip
LF	- Low frequency
MAP	- Mean arterial blood pressure
MVC	- Maximum voluntary contraction
NO	- Nitric Oxide
PEH	- Post-exercise hypotension
PNS	- Parasympathetic nervous system
SBP	- Systolic blood pressure
SNS	- Sympathetic nervous system
SV	- Stroke volume
TP	- Total Power
TPR	- Total peripheral resistance
VLF	- Very low frequency
VSMC	- Vascular smooth muscle cell

CHAPTER 1: Introduction and Literature Review

1.1 Hypertension

1.1.1 Introduction

Hypertension (HT) is a medical condition characterized by sustained levels of high arterial blood pressure (ABP). 1 in 5 Canadians has HT, yet only 43% of people with HT are aware of their condition (39), thus it is often referred to as "the silent killer". HT greatly increases the risk of developing cardiovascular disease (CVD) (89), which is the leading cause of death in Canada (107). HT is directly responsible for 75% of all stroke cases (56). Though significant achievements in the treatment and prevention of HT have been made, the disease remains a prominent health problem in Canada.

1.1.2 Arterial Blood Pressure – Neural, Local and Hormonal Regulation

To better understand the complex pathophysiology of HT, we must first understand ABP itself and the key regulatory mechanisms that sustain ABP in a healthy state.

A complete cardiac cycle (1 beat of the heart) exerts 2 distinct pressures on the body's arterial system: systolic and diastolic. The pressure the blood exerts on the arterial system during a cardiac contraction is known as systolic ABP (SBP). In order for blood flow to occur, it must move from an area of high pressure to an area of low pressure. Therefore, SBP must be greater than the resistance provided by the arterial side of the circulatory system to allow an adequate supply of blood flow to meet the demands and needs of the body's organs and tissues. Diastolic ABP (DBP), however, represents the pressure blood exerts on the arterial system when the heart is in the relaxation phase of the cardiac cycle. These two values are most commonly recorded as SBP/DBP, with normal ABP being ≤120 mmHg /80 mmHg (115).

ABP is a tightly regulated system, maintained primarily through neural, local, and hormonal control. These control mechanisms work together to maintain ABP by influencing 3 main cardiovascular parameters: total peripheral resistance (TPR), heart rate (HR), and stroke volume (SV). Cardiac output (CO) is the product of HR and SV (53), thus changes in CO affect ABP. This is also depicted in the equation for determining ABP, where ABP equals the product of CO and TPR (53).

Neural Control of Arterial Blood Pressure

The neural control mechanism responsible for cardiovascular control, particular ABP, is referred to as "central command" (CC) (97). When the body experiences a cardiovascular stress, CC transmits efferent signals to the cardiovascular control center (CCC), which integrates the signals and responds by changing the balance of the autonomic nervous system (ANS). The ANS can be divided into the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). The SNS has a stimulatory effect on the body, which results in an increase in TPR, HR and SV. The PNS, however, has a relaxing effect on the body. It decreases TPR, HR and SV. These systems work simultaneously, where the upregulation of one system over the other results in physiological changes.

The CCC has a very important role in ABP regulation. Not only does this region receive signals from CC, it also receives afferent signals from receptors located in the body that respond to physiological changes. These receptors include arterial baroreceptors, peripheral chemoreceptors and muscle afferent receptors.

ABP is regulated by the arterial baroreceptors (103). Arterial baroreceptors are stretch receptors located in the arterial wall of the carotid artery at the carotid sinus and aortic arch (19, 57). Since baroreceptors are not pressure sensors, but rather stretch receptors, when pressure exerted on the arterial walls changes, the receptors respond

not directly to the pressure change, but rather to the conformational change the pressure induces in the receptor. The CCC is responsible for receiving and responding to these afferent impulses, which adjusts the ANS to maintain homeostasis.

Peripheral chemoreceptors are sensory receptors responsible for detecting low oxygen levels in arterial blood (31, 94), as well as high carbon dioxide and hydrogen ion concentrations (31). These receptors are located in the carotid and aortic bodies and send afferent signals to the CCC when these conditions occur. The CCC responds to these signals by altering the ANS, increasing the influence of the SNS to increase ABP, in order to sustain adequate levels of oxygen and decrease levels of carbon dioxide and hydrogen ions (31).

Muscle afferent sensory receptors are activated mainly during exercise and send afferent signals to the CCC to alter autonomic activity (46). There are two main sensory receptors: 1) mechanoreceptors, which detect stretch in the contracting muscles and 2) metaboreceptors, which detect metabolic changes within the tissue (71). Mechanoreceptors and metaboreceptors send afferent signals to the CCC, which in turn alter the ANS to regulate ABP (71).

Neural regulation of ABP involves many sensory receptors that communicate with the CCC to alter the ANS. These systems work together to maintain ABP homeostasis and continue to supply the body with adequate blood flow during times of cardiovascular stress.

Local Control of Arterial Blood Pressure

Local regulation of ABP involves vasoactive substances that alter blood flow to meet the metabolic demands of a tissue/muscle (33). Three prominent vasoactive

regulators responsible for these changes are potassium, adenosine triphosphate (ATP) derivatives, and endothelium-derived substances.

Potassium is a substance known to accumulate in the muscle during exercise and slight elevations of potassium have been shown to cause vasodilation, thus causing increased blood flow to target tissues (33). Potassium is a metabolic byproduct released from active muscles. Therefore, its accumulation in the muscle's extracellular fluid is a signal to the smooth muscle to allow an increase in blood flow to compensate for the increased metabolic demands of the tissue.

Derivatives of ATP, including adenosine diphosphate (ADP), adenosine monophosphate (AMP) and adenosine, are all vasoactive substances (33). As ATP is an essential component in muscle contraction, by-products of its catabolism signal an increased demand for blood in the exercising muscle. Therefore, when concentrations of these compounds accumulate, they cause vasodilatation of the vasculature, which increases blood flow to the exercising muscle (33).

Vascular smooth muscles cells (VSMCs) play an important role in ABP regulation. These cells control vascular tone via dilation and constriction, thus altering blood flow and TPR throughout the body. VSMCs form the second layer of the artery (tunica media), and lay adjacent to the endothelium (inner layer or intima; see Figure 1), and are controlled involuntarily (34,116), primarily by the autonomic nervous system. Hormones (e.g., catecholamines, atrial natriuretic factor) and other local chemical stimuli (e.g., NO, endothelin) may also modulate the contractile state of the VSMCs (116).
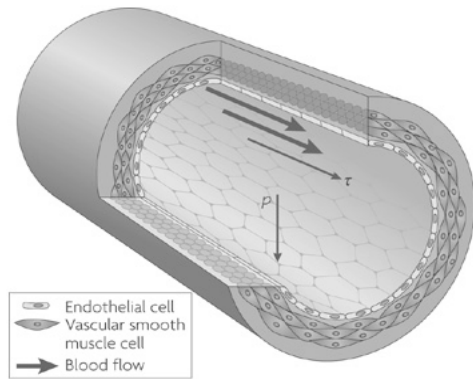
Figure 1: The cellular arrangement of an artery- endothelial cells comprise the inner layer or lumen of the artery (tunica interna, intima) and the second cell layer is composed of vascular smooth muscle cells.

With respect to the latter, NO plays a role in locally-mediated vasodilation. NO is the most potent of the vasoactive substances (109). NO is released by the endothelium in response to shear stress exerted on the blood vessel walls or the presence of a chemical stimulus (catacholamines). NO increases the concentration of cyclic guanine monophosphate (cGMP), which in turn activates cGMP-dependent protein kinase. This protein dephosphorylates the myosin light chain (MLC) of the smooth muscle, which inhibits the binding of myosin and actin, thus preventing contraction and promoting relaxation of the VSMCs (116). Therefore, NO causes a cascade of events that leads to the relaxation of the VSMCs, which in turn allow the blood vessel lumen to expand. This expansion decreases the pressure exerted on walls of the blood vessels, and thus decreases resistance in the vasculature and increases blood flow.

The vasodilatory effects of NO are counterbalanced via the action of vasoconstricting substances, the most powerful of which is endothelin (ET-1; the smooth muscle isoform). ET-1 is a compound released by the endothelial cells in response to a mechanical (i.e., shear stress) or chemical (i.e., angiotensin II) stimulus. There are specific receptors on the VSMCs that bind ET-1: ET_A and ET_B. When ET-1 binds to either of the two receptors on the VSMCs, a cascade of events occurs (93). For

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example, ET-1 induces vasoconstriction via ET_A receptor activation. The binding of ET-1

to its receptor causes the activation of phopholipase C (PLC). Active PLC hydrolyzes the

membrane bound protein phosphatidylinositol into two molecules: inositol triphosphate

(IP_3) and diacylglyerol. These molecules are classified as secondary messengers, as

they relay the extracelluar signal to the inside of the cell. IP_3 binds to the sarcoplasmic

reticulum and causes it to release sequestered Ca^{2+}. ET-1 activates voltage dependent

Ca^{2+} channels on the plasma membrane causing them to open and allow an influx of

Ca^{2+} into the VSMC (93). The contractile state of the VSMCs depends on intracellular

$[Ca^{2+}]$ (116). When intracellular $[Ca^{2+}]$ increases, calmodulin and Ca^{2+} bind to create a

Ca^{2+}-calmodulin complex. This complex activates myosin light chain (MLC) kinase, which

phosphorylates light chain myosin of the VSMCs (115). MLC phosphorylation allows

cross-bridge formation with actin. Myosin ATPase then breaks the high phosphate bond

of ATP, releasing energy and thus allowing smooth muscle contraction to occur (116).

ET-1 also acts via a negative feedback mechanism, whereby the stimulation of

ET_B receptors, located on the endothelium, triggers the release of NO (93). This

feedback response causes the dephosphorylation of the MLC and thus promotes

relaxation of the vasculature.

Hormones and other chemical stimuli are also able to inhibit/promote the activity

of MLC kinase and MLC phosphotase. For example, norepinephrine is considered a

vasoconstrictor, as it promotes the release of Ca^{2+} from the sarcoplasmic reticulum,

promoting Ca^{2+}-calmodulin binding, which in turn causes smooth muscle contraction

(116). In contrast, atrial natriuretic factor (ANF) is classified as a vasodilator as it inhibits

the myosin-actin contractile mechanism and thus promotes vessel relaxation (116).

Hormonal Control of Arterial Blood Pressure

Many hormones influence the control of ABP; including catacholamines (released by sympathetic and parasympathetic neurons), renin (released by the kidneys), aldosterone (secreted by the adrenal cortex), vasopressin (released by the pituitary gland), and atrial natriuretic peptide (released by the heart). These hormones work in conjunction with the neural and local ABP control mechanisms to maintain ABP homeostasis.

SNS neurons release epinephrine and norepinephrine (catecholamines; neurotransmitters), to stimulate specific cardiovascular responses. Where nerve fibers come into close contact with the vasculature, synapses are formed. Norepinephrine is released from the neuron at this synapse. When efferent impulses to these neurons increase, more norepinephrine is released into the synaptic cleft. Norepinephrine travels across the synaptic cleft and binds to vascular α-adrenergic receptors, causing vasoconstriction of the target cell (110). Though some of this compound binds to receptors on the target cell, it is a fraction of the total amount released from the presynaptic terminal. Most of the compound undergoes reuptake by the neural terminal, while another fraction enters the circulatory system. There are also receptors on the presynaptic terminal that are sensitive to norepinephrine. When there is an excess release of this neurotransmitter, some binds to the α2-adrenergic receptors located on the neuron, and further release of norepinephrine is inhibited. This negative feedback response indirectly causes vasodilatation (84).

The outcome of epinephrine release is mediated by the type of receptor to which it binds and the location of the receptor. Both α and β-adrenergic receptors respond to epinephrine. The cardiac response to epinephrine is induced by the stimulation of β-adrenergic receptors. This stimulation will result in increased force of contractility and

increased HR, which therefore increases ABP (70). Vascular α-adrenergic receptors can also be stimulated by epinephrine, which results in vasoconstriction. This causes an increase in TPR, which results in an increase in ABP (70).

HR is also regulated by catecholamine activity. As the amount of norepinephrine released during the stimulation of sympathetic neurons only changes cardiac behavior fractionally, this pathway requires the activity of secondary messengers, cAMP (32). Once cAMP is formed, it stimulates β-adrenergic receptors, which causes the sinoatrial node to increase the rate of impulse generation, thus increasing HR (84). This increase in HR results in an increase in ABP.

The parasympathetic neurons have only a small effect on vascular resistance. These nerves only innervate blood vessels in the sacral and cranial regions of the body, which results in little influence by these neurons (57). Therefore, TPR created by this vasculature only minimally affects ABP.

Acetylcholine is the neurotransmitter released from parasympathetic nerves. When acetylcholine binds to muscarinic receptors, located in the cardiac cell membrane, it causes a decrease in myocardial contractility (8). A decrease in force production by the myocardium results in decreased ABP. Binding of acetylcholine does not directly decrease myocardial contractility, but rather inhibits adenylyl cyclase (8). This causes intracellular cAMP concentrations to decrease, which reduces calcium channel phosphorylation, causing less calcium channels to open (8). This results in a smaller influx of calcium, which in turn reduces the amount of calcium released from the sarcoplasmic reticulum via calcium induced calcium release. This cascading effect ultimately decreases myocardial contractility. HR is also influenced by parasympathetic activity. The stimulation of the parasympathetic nerves releases acetylcholine into the heart, slowing the rate of depolarization. A slower depolarization rate causes HR to

decrease, resulting in an ABP reduction (114). The sinoatrial node can also become hyperpolarized when stimulated by parasympathetic nerves. This results in the sinoatrial node taking a longer time to reach threshold potential, thus slowing the rate of depolarization and therefore decreasing HR and ABP.

The kidneys are recognized as having the most control over long-term ABP regulation. They accomplish this through blood volume regulation and vascular tone. Renin begins the cascade effect by which hormones modulate this system (115).

Renin is a glycoprotein enzyme synthesized in the kidneys. Renin is secreted, via exocytosis, and interacts with angiotensinogen. Angiotensinogen is cleaved by renin to form angiotensin I. Angiotensin converting enzyme cleaves angiotensin I, which is the inactive form of the protein, into angiotensin II, which is the active form of the protein (11). Angiotensin II is a potent vasoconstrictor, and thus will have the effect of increasing ABP by increasing TPR.

Angiotensin II stimulates the secretion of aldosterone from the adrenal cortex. The kidney responds to aldosterone by increasing the reuptake of sodium by the body (70). When sodium is retained, water follows this change in ion concentration, increasing fluid volume in the body. This will have a net effect of increasing blood volume, which will increase ABP.

Thirst is a mechanism by which the body is able to influence fluid intake to increase or decrease total blood volume. As blood volume contributes to ABP, thirst can play a role in ABP. The hormone responsible for the stimulation of thirst is angiotensin II. Once again, this hormone acts to increase ABP by means of increasing fluid intake. Arterial baroreceptors have an inhibitory effect on thirst, which helps to decrease ABP (69).

When ABP is below normal values, vasopressin is released into systemic circulation by the pituitary gland (41). This hormone has 2 specific roles in regulating ABP. First, it is able to induce vasoconstriction in the arteries. As discussed earlier, vasoconstriction of the arteries will cause ABP to increase. The second role of vasopressin is fluid balance regulation (18). Vasopressin changes fluid balance by increasing the amount of water excreted by the kidneys.

There are multiple types of receptors with which vasopressin can interact. 2 receptors are of primary concern, as their stimulation induces changes in ABP. V_1 and V_2 are the receptors of interest. V_1 vascular- termed V_1R- is located in the smooth muscle cells of the vascular tissue. The stimulation of these receptors causes vasoconstriction of the vasculature. V_2 renal- termed V_2R- is located in kidney cells and stimulation of these receptors causes an increase in water excretion into the urine (42). When water excretion increases, total fluid volume within the body decreases, and subsequently ABP decreases.

Cardiac atrial cells release atrial natriuretic peptide when the atria experience an increase in pressure (114). Atrial natriuretic peptide has the opposite effect of aldosterone. This peptide acts on the kidneys to decrease sodium reabsorption. The efflux of sodium will pull water into the urine, allowing the kidneys to decrease blood volume to alleviate rising ABP (70). Atrial natriuretic peptide also has an inhibitory effect on other hormones. Renin, aldosterone and vasopressin secretion are inhibited by atrial natriuretic peptide. This inhibition results in a decrease of ABP (4).

1.1.3 Methods of Measuring Arterial Blood Pressure

The most accurate way to measure ABP requires an invasive procedure. A catheter is inserted into an artery, where a direct continuous intra-arterial measurement can be acquired. However, as intra-arterial catheter ABP measures require medical

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expertise and often incur side effects such as pain, arterial damage, infection, and/or edema (48, 88), the technique is not practical in most settings. As a consequence, numerous indirect ABP measurement techniques have been developed and validated, including: ausculatory sphygmomanometry, osciollometry, and arterial tonometry.

Ausculatory Sphygmomanometry

The gold standard indirect method of measuring ABP involves the use of a sphygmomanometer. In this method, an inflatable cuff is placed around the upper arm, approximately 2-3 cm above the brachial artery (6). The cuff is inflated to a pressure greater than SBP, usually around 200 mmHg. This ensures cessation of blood flow through the artery. Air is slowly released from the cuff. A stethoscope placed over the brachial artery allows the health care professional to detect auditory changes in the artery. As the pressure in the cuff drops below SBP, around 120 mmHg in normotensive individuals, Korotkoff sounds can be heard (57). As the cuff deflates further and the pressure on the artery decreases, more blood is able to flow through the artery, and the sounds become increasingly louder until they disappear. The sound disappears when the pressure of the cuff falls below DBP, which represents complete flow of blood through the artery. This usually occurs around 80 mmHg in individuals with normal ABP (57). This method measures the pressure within the cuff, not the pressure of the artery itself and hence is an indirect method (99). This popular method, however, has inherent limitations, including observer error (particularly the reliance on the observer's hearing), improper cuff size (which measures ABP inaccurately), and incorrect measurement techniques (which result in incorrect values for ABP) (82). This technique requires specialized training to limit the previously addressed limitations.

Osciollometry

Osciollometry is another form of indirect ABP measurement and employs the same preparatory steps of placing a cuff around the upper arm, as described above. This method does not, however, rely on auditory feedback to determine ABP. Rather, it relies on oscillatory signals to estimate ABP (101). As pressure in the cuff decreases, oscillatory signals are collected by a microprocessor within the cuff. Oscillatory signals begin above the value of SBP and cease below the value of DBP. The maximal oscillatory signal the device detects is equal to the mean ABP, which is an average of SBP and DBP (102). The microprocessor applies algorithms to this maximal signal to calculate SBP and DBP (101). This method only estimates SBP and DBP, and thus may result in inaccurate measurements of both values.

Arterial Tonometry

Arterial tonometry also measures ABP non-invasively. This technique allows for the continuous collection of the arterial pressure waveform, giving insight into the continuous fluctuations in ABP during a cardiac cycle (63). Instead of using a cuff to occlude blood flow in the brachial artery (as seen with the previous 2 methods), a pressure sensor is placed on a superficial artery (usually the radial artery (71), which lies on top of a bone. The principle of arterial tonometry is dependent upon the artery in question being compressible (35). In order to obtain an accurate pressure waveform, the pressure sensor must adequately flatten the artery. The Imbert-Fick law states the internal pressure of a completely elastic spherical body equals the force exerted on this body, divided by the flattened surface. This law allows for arterial tonometry to estimate ABP (63). Though this technique gives insight into continuous ABP, it does have some limitations: positioning of the device must be precise, motion artifacts can interfere with

the signal, and calibration of the device requires the use of an external measurement (63).

1.1.4 Pathophysiology and Consequences of Hypertension and Recommendations for Treatment

HT is defined as a sustained elevation of resting ABP. ABP can be categorized as normal, pre-HT and HT. Normal values for SBP are ≤120 mmHg and ≤80 mmHg for DBP (15, 105). A person is classified as having pre-HT when their SBP ranges between 120 -139 mmHg and/or their DBP ranges between 80-89 mmHg (15, 105). HT is classified as a SBP ≥140 mmHg and/or DBP ≥90 mmHg (15, 105). Stage 1 HT is defined as SBP between140 - 159 mmHg and/or DBP between 90 - 99 mmHg and Stage 2 HT as a SBP ≥160 mmHg and DBP ≥100 mmHg (15, 20).

HT can be of known or unknown causes. Essential (primary) HT encompasses 95% of all cases of HT and the cause is unknown (20). In contrast, systemic (secondary) HT has a known cause, yet only accounts for a small percentage of all cases (20). As previously discussed, ABP is regulated through neural, local and hormonal control. A problem in one or more of these regulatory systems may contribute to the development and maintenance of HT. Essential HT tends to be genetically linked, where salt sensitivity, renin secretion, and obesity can be potential contributors to the pathophysiology of HT (20). This form of HT can be treated and/or prevented with lifestyle modifications (exercise and diet) and/or with pharmacological treatment (20). Systemic HT is unique in that it can be directly related to a specific physiological problem. For example, HT is often caused by problems occurring with the endocrine and renal systems and/or can be improved or even cured through medical therapy or surgery (20).

The pathophysiological manifestations and consequences of HT lead to pre-mature death in treated and untreated individuals (20). The risk of developing CVD doubles for every incremental increase of 20 mmHg and 10 mmHg in SBP and DBP, respectively (14). HT is mostly associated with increased TPR and normal CO (20).

HT can cause endothelial damage, which is believed to contribute to the development of vascular diseases, including atherosclerosis (20). Other outcomes of vascular damage include renal disease and stroke (20). In addition, chronic increases in TPR cause the heart to continually work harder to overcome this higher resistance and adequately perfuse the tissue. This can result in ventricular hypertrophy and dysfunction, and ultimately in overt heart failure (20).

HT is associated with an increase in sympathetic outflow and decreased parasympathetic activity, including a reduced ability of the autonomic nervous system to modulate HR (HR variability; HRV) (111), all of which increase the risk of cardiac mortality (112).

The primary prevention and treatment recommendations for HT include lifestyle modifications such as diet modification and exercise prescription, particularly in pre-HT individuals (15). Increased physical activity and dietary changes alone have been shown to reduce ABP and bring ABP to within the normal range (15). Other lifestyle modifications include maintaining a normal weight, decreasing dietary sodium intake, limiting alcohol intake, and following the Dietary Approaches to Stop Hypertension (DASH) eating plan (a diet containing a large amount of vegetables, fruit and low-fat dairy products) (15). In some individuals, following the DASH eating plan has been shown to be as effective as a single anti-HT medication (15). Therefore, lifestyle modification plays a vital role in the management and prevention of HT.

Pharmacotherapy is often prescribed if lifestyle modifications alone fail to decrease ABP to within the normal range (or ABP is morbidly elevated). There are many medications prescribed to treat HT and depending on the severity of the HT, more than one medication may be needed to adequately control ABP (15). The main classes of HT medications are: diuretics, angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), β-blockers (BBs), and calcium channel blockers (CCBs) (15).

Diuretics are recommended as the first type of pharmacological intervention, as they reduce cardiovascular complications associated with HT (15). The antihypertensive effects of diuretics are attributed to alterations in kidney function including: increasing the excretion of chlorine, sodium, potassium and bicarbonate ions in the urine, inhibiting the reuptake of sodium and chlorine ions by the kidneys, and decreasing uric acid and calcium excretion in the urine (20).

ACEIs are effective in lowering ABP by preventing the conversion of angiotensin I to angiotensin II, which as previously described, is a potent vasoconstrictor (20). Reduction of circulating angiotensin II decreases vasoconstriction, which in turn reduces TPR and therefore, ABP. Individuals with diabetes are usually prescribed ACEI medications to protect their kidneys, as diuretics interfere with the normal functioning of the kidneys (20).

ARBs evoke similar outcomes to ACEIs because they block angiotensin II from binding to its receptors (20). ARBs inhibit aldosterone secretion and the vasoconstrictive effects of angiotensin II (20). Inhibition of aldosterone decreases blood volume, while decreasing vasoconstriction decreases TPR. Both of these outcomes result in TPR reductions.

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BBs are another type of medication prescribed to lower ABP. These medications compete with epinephrine for the binding site on β-receptors (20). When BBs bind, they prevent epinephrine from stimulating the sinoatrial node to increase HR. Ultimately they decrease the force of cardiac contractility and HR, which result in a reduction of ABP (20).

The most common class of CCBs used to treat HT are collectively named dihydropyridine CCBs (20). These types of CCBs act on the smooth muscles in the vasculature. They induce vasodilation by inhibiting the calcium influx into smooth muscle that causes vasoconstriction (20). The antihypertensive effect of this medication is a result of decreased TPR, and thus decreased ABP (20). A potential side effect of these medications is an increased in HR due to the rapid vasodilation of the vasculature (20). To avoid such complications, long-acting agents are preferred, as they result in gradual vascular changes, and prevent the rapid activation of the SNS (20).

Recent evidence suggests that although chronic pharmacotherapy can reduce ABP to within the normal range, individuals still exhibit high levels of sympathetic outflow (28), despite this adequate ABP control. This high level of sympathetic outflow may explain the high rates of morbidity and mortality in individuals medicated for HT (28).

In 2007, it was estimated that Canadians spent over $26 billion dollars on pharmaceuticals (10), with 20% of this spending accounting for hypertensive medications (77). While medication is effective in the treatment of HT, mortality rates in the HT population remain high. Furthermore, pharmacotherapy is effective in less than 50% of treated patients (74), leaving many unanswered questions surrounding the effectiveness of pharmacotherapy.

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1.2 Exercise and Hypertension

Exercise effects acute and chronic ABP regulation. As described in the previous section, physical activity can reduce chronic resting ABP, while the acute alterations in ABP occur to maintain muscle perfusion and activity. Exercise plays a large role in the prevention and management of HT, as previously discussed (20). The American College of Sports Medicine (ACSM) recommends aerobic exercise 3 to 7 times per week for 30 to 60 minutes at an intensity of 30 (for sedentary individuals) to 85% (for regular vigorous exercising individuals) of an individual's oxygen reserve to elicit the health benefits associated with exercise training (2). Resistance exercise is recommended as a supplement to this aerobic activity (2). The ACSM recommends resistance exercise be performed 2 to 3 times per week, where one set of 10-15 repetitions are performed for each of the major muscle groups (20). Currently, there are no ACSM-endorsed recommendations for chronic isometric exercise training.

1.2.1 Effects of Acute Exercise on Arterial Blood Pressure
Aerobic Exercise

Aerobic exercise (walking, running, swimming, cycling) involves the rhythmic contraction of muscles for a sustained period of time. At the onset of aerobic exercise SBP increases linearly, and during high intensity exercise, can reach values of > 200 mmHg (54, 65). This increase in SBP is due to an increase in HR, CO, and blood flow to insure adequate perfusion of the active muscle (55). The pressor reflex (efferent muscle signals which causes constriction of the arterioles) also contributes to the rise in ABP. Active muscles respond to this increase in SBP through vasodilation, helping offset the rise in ABP (53). This results in a decrease in TPR, to levels less than at rest (53). As such, SBP does not remain high for the duration of the exercise, and generally

normalizes around 140-160 mmHg (65). As a result of TPR reductions, DBP changes minimally with aerobic exercise (65).

Resistance Exercise

Resistance exercise involves both static and dynamic exercise. During the static portions of the exercise, SBP/DBP have been shown to increase to values above 400/200 mmHg (20). Resistance exercise affects many cardiovascular parameters including HR, SV, (thus CO) and blood flow (64). As with aerobic exercise, these parameters change depending on the intensity of the exercise.

During the concentric/eccentric portion of the exercise, blood flow to the contracting muscle is occluded, due to the mechanical compression of the vasculature (64). This occlusion causes the ANS to stimulate the SNS to increase CO, which results in an increase of ABP (64). Other contributors to the increase in ABP include the pressor reflex and the Valsalva maneuver (breath holds and/or forced exhalations against a closed airway). The Valsalva maneuver causes an increase in intrathoracic pressure, which results in an increase in ABP (58). The magnitude of ABP increase is directly related to the size of the contracting muscle, thus larger muscle masses induce larger changes in ABP (65).

Isometric Exercise

Acute bouts of isometric exercise (sustained voluntary contraction of a muscle) have a unique effect on the cardiovascular system. At the onset of isometric exercise, increased HR, CO and sympathetic outflow are responsible for the initial increases in SBP and DBP (50, 62).

Isometric muscle contraction results in occlusion of blood flow to the working muscle, as a result of the compression of the vasculature (62, 64). This induces the

pressor reflex, which increases sympathetic nervous activity, resulting in an increase in HR and CO, to ensure adequate blood flow to the contracting muscle (62). If the Valsalva maneuver is executed, ABP will further increase, due to the increase in intrathoracic pressure (58).

As muscle force increases, the intensity of the exercise also increases, resulting in higher levels of ABP (53). The increase in ABP, however, is greater than the ABP needed to meet the metabolic demands of the working muscle by ensuring adequate muscle perfusion (53). Both increasing the size of the muscle mass performing the isometric exercise, and increasing exercise duration, influence ABP directly (53). With isometric exercise, however, ABP never reaches a steady state, but continues to increase (53).

1.2.2 Post-Exercise Hypotension

Post-exercise hypotension (PEH) is a unique phenomenon characterized by a sustained reduction in resting ABP after an acute bout of exercise (85). PEH can be observed for up to 22 hours following an exercise bout (89). This event is most pronounced in individuals with HT (59). The average short-term PEH reductions in resting SBP and DBP are ~15 mmHg and ~4 mmHg, respectively (89).

PEH has predominantly been investigated following bouts of aerobic exercise (59). Although there is evidence to suggest that resistance exercise elicits a PEH response; this finding is somewhat equivocal and not without controversy (23, 59) For example, some studies have shown a prolonged reduction in SBP, but no prolonged reduction in DBP (63, 64). A study conducted by O'Connor and colleagues (1993) found no prolonged reduction in ABP following resistance exercise. It is thought that the observed reductions in ABP post-resistance exercise may simply be due to the

reperfusion of blood to the working muscles that were previously occluded during muscle contraction (59). As PEH is described as a prolonged event and as such, some feel that should not be confused with these described reductions in ABP immediately following resistance exercise (59).

Consensus in the literature suggests that the mechanisms responsible for PEH acute bouts of aerobic exercise are decreased vascular resistance and a decrease in sympathetic nerve activity (17, 26, 36, 44, 59, 85). As previously noted, ABP is the product of CO and TPR. Therefore, if a decrease in sympathetic nerve activity occurs, there will also be a decrease in TPR and CO (including HR and SV). It could possibly be the decrease in sympathetic nerve activity that is responsible for the decrease in vascular resistance, which would allude to decreased sympathetic nerve activity being responsible for PEH. The effects of isometric exercise on PEH are unknown.

1.2.3 Effects of Exercise Training on Arterial Blood Pressure

<u>Aerobic Exercise Training</u>

A number of meta-analyses collectively affirm that aerobic exercise training, using a variety of exercise modalities (walking, running, cycling), frequencies (1 to 7 days/week), durations (30-60 minutes) and intensities (30 to 90% maximum oxygen consumption), reduces resting ABP in both HT and normotensive individuals (89). Participants in these studies were between the ages of 18 to 79 years, demonstrating the effectiveness of aerobic training in reducing ABP throughout the lifespan (89).

Overall, normotensive individuals showed average reductions of 2.6 mmHg and 1.8 mmHg for SBP and DBP, respectively, while HT individuals exhibited larger average reductions in ABP, with SBP decreasing by ~7.4 mmHg and DBP decreasing by ~5.8

mmHg following training (89). The observed differences in total SBP and DBP reductions are most likely the result of initial differences in ABP values.

The specific mechanisms by which aerobic training alters ABP remains elusive, however, it is thought that an alteration in TPR, rather than CO, is responsible for this change (89). Vascular changes (e.g., increased endothelial-dependent mediated vasodilation), structural changes (e.g., increased cross-sectional area of resistance vessels), and functional changes (e.g., norepinephrine receptor desensitization and increased NO availability and release) are all likely candidates for aerobic training adaptations (89). Neural modifications (decreased sympathetic nerve activity) and genetics may also play a role in aerobic training adaptation (89).

Resistance Exercise Training

A meta-analysis completed by Kelley and Kelley (2000), analyzed resistance-training data from 11 randomized control trials. They found only small overall reductions in ABP, with a 2 - 4 mmHg reduction in SBP and a 3 - 4 mmHg reduction in DBP. However, similar reductions have shown to decrease the risk of stroke and coronary heart disease (47). Resistance training also improves ABP spikes during exercise (64). As an individual becomes more advanced/trained in resistance exercise, they exhibit smaller increases in both SBP and DBP (64).

The mechanisms thought responsible for these ABP reductions following resistance training are similar to those seen with aerobic training (89), such that vascular, structural, functional and neural adaptations may be responsible for altering ABP through inducing changes in TPR (89).

Isometric Exercise Training

Early studies involving isometric exercise training, examined whole-body isometric exercise and the effects of training on resting ABP. Kiveloff and colleagues (1971) observed in unmedicated hypertensives, following 5 to 8 weeks of isometric training, 3 times per week, decreases in SBP of 4 - 28 mmHg and DBP of 2 - 14 mmHg (49).

Later studies investigated the benefits of a simpler isometric training protocol: isometric handgrip (IHG) exercise (118). For example, 8-weeks of IHG training in normotensive individuals resulted in reductions in resting SBP of 12 mmHg and DBP of 14 mmHg. This protocol involved 4 isometric contractions of the dominant arm for 2 minutes, separated by 3 minutes of rest, at 30% maximum voluntary contraction (MVC), performed 3 times per week (85). Ray and colleagues (2000) further supported the effectiveness of IHG training in reducing ABP in normotensive individuals. Using a similar exercise protocol (4 isometric contractions separated by 5 minutes of rest, 4 times per week for 5 weeks) they found significant reductions in resting mean ABP (MAP) of 4 mmHg and DBP of 5 mmHg. Although resting SBP decreased by approximately 3 mmHg, this did not yield statistical significance (85). In 2007, a study examining normotensive individuals and the effects of an 8-week unilateral IHG protocol (consisting of 4, 30% MVC contractions, sustained for 2 minutes with the non-dominant hand, with 4 minutes of rest between contractions) found similar ABP reductions. Investigators reported a 4.9 mmHg reduction in SBP with no significant differences in DBP (66). The clinical impact of IHG training was explored by Taylor and colleagues (2003) who investigated the effects of 10 weeks of IHG training, performed 3 times per week (consisting of 4, 30% MVC contractions, sustained for 2-minutes with alternate hands, each contraction separated by 1 minute of rest) in HT individuals. The findings of this

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study support the benefits of IHG training, showing resting SBP and DBP to decrease by 19 mmHg and 7 mmHg, respectively (111).

McGowan and colleagues (2006) examined the effects of 8 weeks of bilateral (consisting of 4, 30% MVC contractions, sustained for 2 minutes with alternate hands, with 1 minute of rest between contractions) and unilateral (consisting of 4, 30% MVC contractions, sustained for 2 minutes with the non-dominant hand, with 4 minutes of rest between contractions) IHG training protocols in medicated hypertensives. Subjects completed IHG training 3 times per week for a total of 8 weeks. No changes in DBP were found, however, the bilateral training reduced SBP by 15.4 mmHg and the unilateral protocol reduced SBP by 9.2 mmHg. This study demonstrated both bilateral and unilateral IHG training programs are able to reduce SBP.

In 2007, a multilevel analysis was performed to amalgamate 3 previous IHG training studies performed at McMaster University (75). The analysis population involved medicated hypertensives that had performed either a bilateral or unilateral (as described in the previous paragraph) training program for 8 weeks (3 times per week). The results of this multilevel analysis showed combined reductions of 5.7 mmHg and 3.0 mmHg for SBP and DBP, respectively (75).

Most recently, Millar and colleagues examined the effects of IHG training in normotensive individuals (72). They used an 8-week, 3 times per week, bilateral training protocol (as described earlier). This study showed reductions in both SBP and DBP of 10 mmHg and 3 mmHg, respectively. This study further supports the validity that IHG training in an effective exercise to reduce ABP.

1.3. Heart Rate Variability

Autonomic modulation of HR (HR variability; HRV) can be estimated by determining beat-to-beat variations in HR in the time or frequency domain.

Time domain HRV analysis

Common variables used for time domain analysis include, among others, the standard deviation of all normal R-R intervals (see Figure 2) within an established time interval, the standard deviation of beat-to-beat pulse interval variations, and the number of differences of successive R-R intervals (Figure 3) > 50 msec/total number of R-R intervals.

Frequency domain HRV analysis

Spectral analysis is a noninvansive frequency domain method used to estimate contributions of the PNS and SNS to short- and long-term oscillations in HR. The most common algorithms employed for this purpose include fast Fourier transformation (FFT), autoregressive analysis (AR) and coarse-grain spectral analysis (CGSA).
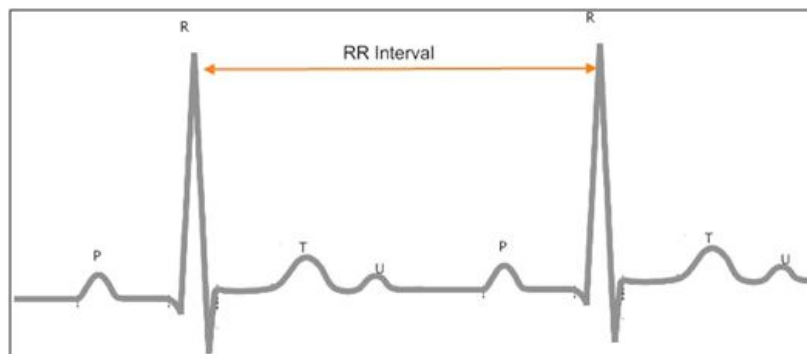
Figure 2- ECG signal- Depicting the R-R interval used to assess HRV (78).
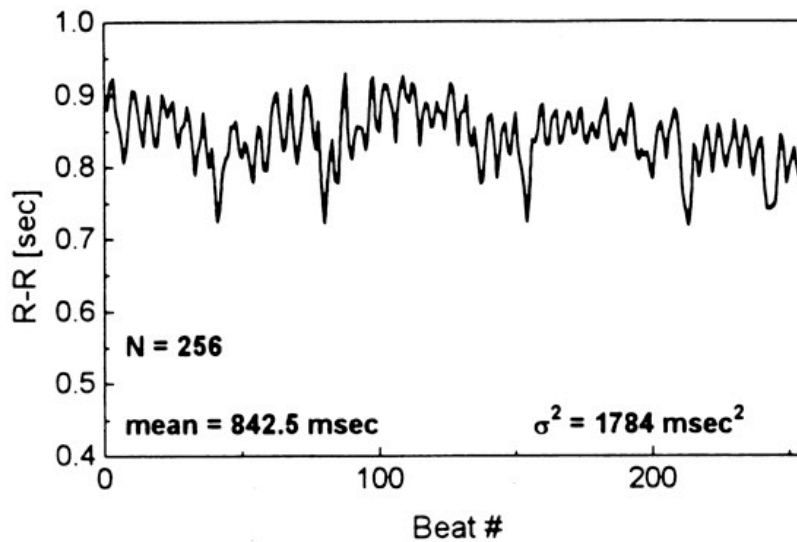
Figure 3: Consecutive R-R Intervals- displays the beat number vs. length of heart beat (R-R) (adapted from 1).

1.3.1 Assessment of Heart Rate Variability

Fast Fourier Transformation

Fast Fourier Transformation (FFT) is a unique form of frequency domain analysis in that the R-R signal is not filtered prior to processing (5, 87). Once the ECG signal is obtained, the signal is subdivided into seven equal segments. Each of the segments is halfway overlapped by adjacent signal segments (37). Signals are often periodic in nature, which leads to the breakdown of the signal into sinusoidal waves (37). Signals are often accompanied by spectral noise that must be eliminated to provide a more accurate analysis. Using the correct parameters is essential because if they are set too small, they do not provide a good representation of the original signal. Alternatively, if the parameters are set too high, the signal is accompanied by a great amount of noise and inaccuracies (92). The signal parameters are determined by applying linear regression analysis to the entire signal, followed by the subtraction of the linear trend from each of the individual 7 segments (3, 37, 51). In order to minimize spectral leakage (loss of data)

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within a finite observation and smooth the spectral signal, windowing functions (spectral analysis; FFT) must be applied (37). The application of a FFT allows the signal to be easily interpreted and evaluated using a graphical representation of the data (5, 37; See Figure 4 (1)). The graphical product of the FFT defines the frequency bands: very low frequency (VLF), low frequency (LF), and high frequency (HF) (3). The LF component provides insight into the sympathetic modulation of HR, while the HF component provides insight into the parasympathetic modulation of HR (5, 111). The VLF component corresponds to non-harmonic noise within the spectrum (111). The ratio of LF: HF can be examined to give insight into the sympathovagal influences contributing to the alterations in HR by the autonomic nervous system (111).

	FREQUENCY Hz	POWER msec^2
VLF	0.00	266
LF	0.10	164
HF	0.25	214

window = Hann
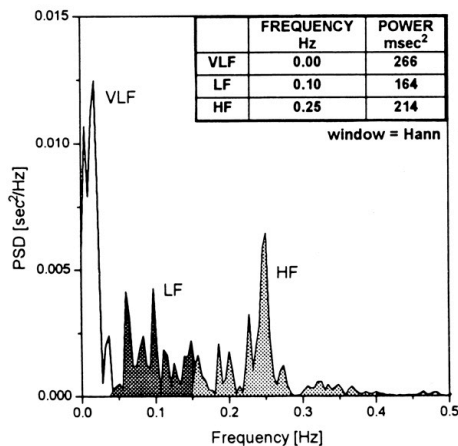
Figure 4: FFT spectral analysis- Depicts the VLF, LF and HF peaks of the signal (adapted from (1)).

Autoregressive Modeling

Autoregression (AR) is a model used to analyze a time series of data (in this case, R-R intervals) to determine the number, center frequency and powers of the oscillatory components (52, 76, 87, 90). Similar to FFT, this method of analysis requires a set of parameters (model order) to establish the frequency spectrum and there are many techniques available (e.g. Akaike Information Criterion) to determine the correct

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parameters (92). Once the parameters have been selected, Burg's algorithm is used to determine the coefficients for AR, which enables power spectrum acquisition (92; See Figure 5). Like FFT, AR defines the following peaks: very low frequency (VLF), low frequency (LF), and high frequency (HF), and thus describes the bands of the power spectrum.

	FREQUENCY Hz	POWER msec^2	POWER n.u.
VLF	0.00	785	
LF	0.11	479	47.95
HF	0.24	450	45.05

LF/HF = 1.06
PEWT > 3
OOT = 9
p = 9
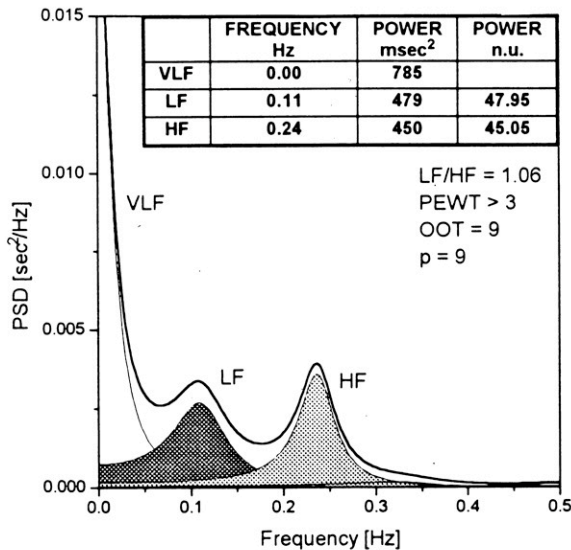
Figure 5: AR spectral analysis- Depicts the VLF, LF, and HF bands of the spectrum (adapted from 1).

In comparison to FFT, AR models create smoother power spectra with better frequency resolution from shorter segments of data, only requiring one or more sinusoidal waves (92). Though FFT and AR models produce similar findings, in individuals with high HRV, AR tends to overestimate LF and underestimate HF powers compared to the FFT model of analysis (16).

Coarse Graining Spectral Analysis

Coarse Graining Spectral Analysis (CGSA) allows for more accurate quantitative analysis by acquiring clearer peaks in the LF and HF components (119). This is

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accomplished by first dividing the total spectral power (TP) into non-harmonic (fractal) and harmonic (oscillatory) components (81). This type of analysis is particularly useful in subjects who have reduced harmonic spectral power and preserved non-harmonic power (i.e., heart failure and hypertension) (81). After the harmonic component is determined, this component is integrated across the LF and HF ranges. The HF integrated range can then be normalized to the TP, determined by dividing HF by TP. The LF: HF ratio gives insight into the autonomic balance in the regulation of HR (119).

1.3.2 Reduced Heart Rate Variability

Reduced HRV increases the risk of cardiac mortality (112). The weight of evidence suggests that individuals with HT have reduced HRV in the time domain compared to normotensive subjects (104). There is also data to suggest that HF power (vagal tone) is reduced (1, 87) and the LF component of the power spectra is augmented in individuals with HT (32, 87) although this latter finding is equivocal. The discrepant findings in the LF power spectra may, however, be accounted for by methodological differences. Reduced HRV is also associated with a number of other CVD risk factors including aging, smoking, and physical inactivity (21), and diminished HF power and increased LF power are prevalent in the CVD population as a whole (21).

1.3.3 Treatment of Reduced Heart Rate Variability

As reduced HRV is a known risk for increased cardiac mortality, the benefits of improving HRV have been speculated upon, however, it is unknown whether improving HRV decreases the risk of cardiac mortality (1). Pharmacotherapy has been investigated as a treatment option for reduced HRV.

BBs have been shown to increase HRV in patients after a myocardial infarction (1). Specifically, the rise of the LF component in the morning hours (due to sleep to wake transition; increase in sympathetic tone) was blunted (1). HRV has been shown to

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increase with a low-dose of muscarinic receptor blockers (Scopolamine, atropine) (1). In both post-myocardial infarction patients and those with chronic heart failure, Scopolamine was shown to significantly increase HRV. Specifically, this medication was shown to increase vagal tone, which could also be observed, as individuals had a decrease in heart rate (1). The large scale and long-term effects of these medications require further investigation (1).

Exercise training, as well as, dietary changes and maintenance of normal weight are commonly employed interventions aimed at improving autonomic modulation of HR (15).

1.4 Exercise and Heart Rate Variability

1.4.1 Effects of Acute Exercise on Heart Rate Variability

The effects of acute exercise on post-exercise HRV have been under-investigated, however, the available evidence supports beneficial changes in HR modulation following a bout of aerobic exercise. For example, Javorka and colleagues (2002) observed increased HF power, decreased LF power and an improved LF/HF ratio following an acute bout of bench step climbs for 12 minutes in healthy normotensive males (43). The authors attributed these findings to an increase in parasympathetic tone upon the cessation of exercise. Raczak et al. (2005) investigated the effects of 30 minutes of constant treadmill exercise on post-exercise HRV. Upon cessation of the exercise, HRV increased (all indices of parasympathetic activity increased) (95).

These results are somewhat equivocal however, as contrary to the findings of the previous 2 studies, other studies have shown decreases in HRV post-exercise. Healthy, normotensive, sedentary men were engaged in both interval (45 minutes) and steady state (time adjusted so participants produced the same amount of work as interval

exercise) cycling exercise (78). Both protocols decreased post-exercise HRV (TP, LF, HF; 78). Masters athletes (men and women; regular cyclers) who engaged in 25 - 35 minutes of incremental cycling until a lactate threshold of 4.5mmol was observed showed a post-exercise decrease in HRV (TP, VLF, LF and HF) compared to pre-exercise indices (9).

The evidence suggests the mode, intensity and duration of exercise play a role in post-exercise HRV, and it can be either improved or reduced after an acute bout of aerobic exercise.

1.4.2 Effects of Exercise Training on Heart Rate Variability

<u>**Aerobic Exercise**</u>

The effects of aerobic training on HRV have been thoroughly investigated (7, 12, 29, 45, 108), and although the findings are somewhat inconclusive, they appear population dependent. Although there is data to suggest an improvement in HRV with aerobic training in patient populations and in older individuals, this has not consistently been demonstrated in young, healthy populations. For example, in a study examining the effects of 8-weeks of endurance-based (static cycling and calisthenics) cardiac rehabilitation on HRV in patients who had experienced a myocardial infarction (61), investigators noted improved HRV, (increase in HF power and decrease in LF power) in the exercise group compared to the non-exercising control group (61). These improvements persisted for 1 year following training, in contrast to the control group, who still experienced reduced HRV after the 1-year period (61). Furthermore, Stein and colleagues (1999), revealed significant increases in HRV (increase in TP, LF and VLF) after a 12-month aerobic training program (3 month initial flexibility training, followed by 9 months endurance exercise (walking, jogging, cycling and rowing), 5 days per week, 45-60 minutes, 60 to 85% VO_2max) in healthy older individuals. These changes may be

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attributed to the population group, as older individuals have decreased HRV, or to the longer duration of training. A more recent investigation determined that, 8 weeks of aerobic training elicited marked increases in HRV (LF power increase (9%) and HF power increased (11%) in post-menopausal women (45) who performed treadmill and/or recumbent cycling (3-4 times per week, 120-165 minutes, at 50% VO$_2$max)) (45).

In contrast, Boutcher and colleagues (1995) found healthy middle-aged individuals who underwent 24 aerobic training sessions (20-30 minutes walking/jogging/cycling, 3 times per week, at 60% HR range) to have no significant alterations in HRV. Similar findings were noted in healthy, young, middle-aged men following 3-months of aerobic training (40 minutes of walking and/or jogging, 3 times per week, 75 to 80% peak HR) (12). Again, no significant post-training changes in HRV were observed in this group (12). This lack of change in HRV may be attributed to the population being examined, as younger individuals have increased HRV compared to their older counterparts.

Resistance Exercise

The effects of resistance training on HRV have been investigated to a lesser degree than aerobic training; however, the results continue to support increases in HRV with exercise in clinical and older populations. In an early study examining the effects of 3 months of resistance training (circuit training, 3 times per week, at a moderate intensity) in persons with chronic heart failure (100), significant increases in HRV were observed (increase in HF power and decrease in LF power). More recently, the effects of 16 weeks of resistance exercise (30 minutes circuit training, 8-12 repetitions, 50-80% of 1 repetition maximum, 2 times per week) were examined in women with Fibromyalgia who had pre-training reductions in HRV (22). Investigators found increased HRV (increase in TP and HF power) after the training program.

Isometric Exercise

Few studies have investigated the effects of isometric training on HRV. In 2003, Taylor and colleagues investigated the effects of 10 weeks of IHG training on HRV in hypertensive individuals (3 times per week, 4, 30% MVC contractions, sustained for 2-minutes with alternate hands, separated by a 1 minutes rest period). This study further supports the benefits of exercise training on HRV in clinical populations, as the investigators observed improvements in HF power following the training period (111).

1.5 Ambulatory Blood Pressure and the effects of Exercise Training

Ambulatory ABP gives insight into the 24-hour fluctuations of ABP, and is reflective of activities of daily living. Although controversial, diagnostic clinical ABP measurements appear to inaccurately estimate resting ABP, and 40% of the time these readings are incorrect, as compared to 24-hour ABP measurements (38). Furthermore, ambulatory ABP is more efficacious in predicting CVD related events than clinical resting ABP measures (91). The benefits of ambulatory ABP monitoring have made this practice an increasingly popular tool in the clinical setting (91).

The mean ambulatory values for ABP in normotensive individuals are 135 mmHg and 85 mmHg (91) for SBP and DBP, respectively, although ambulatory ABP in normotensive individuals do have diurnal rhythms. These diurnal rhythms can also be observed in many individuals with HT, however, the ABP mean values in this population are increased overall (91). Ambulatory blood pressure is highest during the morning hours (attributed to the change from a sleep to a waking state) and lowest (10 - 20% lower) during the sleeping hours (91).

The effects of exercise training on ambulatory ABP have been underinvestigated. Van Hoof and colleagues (113) found healthy males who performed endurance exercise

for 4 months experienced reductions in daytime DBP by ~5 mmHg. Ambulatory ABP was shown to decrease by 4.8 mmHg and 7.5 mmHg for SBP and DBP, respectively, in mild and borderline HT individuals after 6 months of endurance training (106). Palatini and colleagues (86) also examined the role of exercise training in ABP. Unmedicated HT individuals (86) were divided into an exercise training group and a control group by self-reported indices of exercise. If subjects reported to participate in aerobic sports, at least 1 time per week, they were included in the training group, and those who did not partake in such activities, were assigned to the control group (86). Results showed similar SBP values between the training and non-training groups, however, the training group exhibited lower DBP (4 mmHg). The training group also had smaller differences in both day and night ambulatory ABP than the control group (86).

A meta-analysis of 11 studies, conducted by Cornelissen and Fagard in 2005, examined the effects of ≥ 4 weeks of exercise training (walking, running, cycling) on ambulatory ABP (13). Daytime SBP and DBP decreased by 3.0 mmHg and 2.4 mmHg while nighttime ABP decreased 3.3 mmHg and 3.5 mmHg for SBP and DBP, respectively (13). This study reaffirmed the previous studies, showing endurance exercise can significantly decrease ambulatory ABP in both normotensive and hypertensive individuals.

1.6 Summary of Background

CVD is the leading cause of death in Canada, with HT significantly contributing to the risk of its development. HT is a complex pathophysiological disease, which rarely can be attributed to a known cause. Individuals with HT have elevated resting and ambulatory ABP, experience PEH following many forms of exercise, and have reduced HRV.

The prevention and treatment of HT include lifestyle modifications and pharmacotherapy. Many individuals treated with pharmacotherapy remain above the normal ABP range, yet others remain unaffected. Lifestyle modifications, particularly exercise, have proven to be a successful means of lowering resting and ambulatory ABP and improving HRV. IHG training is a novel, non-time consuming, and simple form of exercise, shown, in individuals with and without HT, to markedly reduce resting ABP. The transfer of these effects to activities of daily living (i.e., ambulatory ABP), however, is currently unknown. Furthermore, individuals with HT have shown improvements in HRV with IHG training; however, the PEH and HRV response post-IHG bout remain unknown, as are the effects of IHG training on these responses.

1.7 Thesis Objectives

The objectives of this thesis project are 2-fold:

1. To investigate the ABP (PEH) and HRV responses immediately following a bout of IHG in individuals medicated for hypertension, and to observe the effects of training on these responses,

2. To replicate previous reductions in resting ABP and improvements in HRV, and observe the effects of training on 24-hour ambulatory ABP,

1.8 Specific Hypotheses

The substantive hypotheses are:

1. HT individuals will experience PEH following an acute bout of IHG exercise accompanied by an increase in vagal modulation in HR, prior to training, and it is expected that these responses will be altered after 8 weeks of training.

2. Resting and ambulatory ABP will decrease with 8-weeks of bilateral IHG training, and resting HRV will improve with training.

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CHAPTER 2: General Methodology

2.1 Overview

The general methodology chapter provides an overview of the methods used to study **the effects of isometric handgrip exercise on post-exercise hypotension, ambulatory arterial blood pressure and heart rate variability in individuals medicated for hypertension**. Although the data was collected in one large study, for the purposes and ease of knowledge translation and publication, the data has been separated, and will be presented as 2 manuscripts.

The first, entitled: **Acute effects of IHG exercise on arterial blood pressure and heart rate variability in medicated hypertensives and the influence of training,** and described in detail in Chapter 3, was designed to examine two research questions: 1) Does an acute bout of IHG cause sustained reductions in ABP and improvements in HRV (specifically improved vagal modulation of heart rate)? and, 2) Does 8-weeks of IHG training attenuate the acute ABP and HRV responses following a single bout of IHG exercise? In order to answer the proposed questions, 11 participants trained 3 times per week for 8-weeks, and 9 individuals served as non-trained ABP controls. Measures of pre-IHG ABP and HRV, and post-IHG ABPs and HRV were acquired for all participants at baseline, after 4 weeks of training or control ABP measures (mid-training; week 5), and following 8 weeks of training or control ABP measures (post-training; week 9).

The second, entitled: **Effects of isometric handgrip training on resting and 24-hour ambulatory arterial blood pressure and heart rate variability in individuals medicated for hypertension,** and described in detail in Chapter 4, was designed to examine two research questions: 1) Does 8-weeks of IHG training reduce resting and ambulatory ABP in medicated hypertensives? and, 2) Does IHG training improve HRV in individuals medicated for hypertension? Eleven individuals trained 3 times per week for 8-weeks, and 9 participants served as non-trained ABP controls. Measures of resting

and ambulatory ABP and HR were acquired for all participants at baseline, after 4 weeks of training or control ABP measures (mid-training; week 5), and following 8 weeks of training or control ABP measures (post-training; week 9).

The general methodology chapter includes descriptions of the study participants, the large-scale study design, the IHG training protocol, and the testing methodologies. These include pre- and post- ABPs and HRV measures, resting ABP, and ambulatory ABP.

Comprehensive details regarding the study participants, data collection and analyses protocols, and statistical analyses for the above-noted manuscripts are described in each of Chapters 3 and 4.

2.1.1 Study design

The University of Windsor Research Ethics Board approved this randomized controlled study (REB# 09-060; Appendix D). After inquiring about the study, participants were required to meet with study investigators (Physical Activity and Cardiovascular Research (PACR) laboratory, Room #240, Human Kinetics Building, University of Windsor, Windsor, ON, Canada) for an informational meeting and to sign a letter of information (Appendix E), an informed letter of consent (Appendix F) and a medical questionnaire (Appendix G). Upon review of the medical questionnaire and establishment of eligibility, participants returned to the PACR laboratory (Room #240, Human Kinetics Building, University of Windsor, Windsor, ON, Canada) to undergo familiarization of all testing procedures.

Following habituation, participants were randomized to the IHG training group or the non-exercising control group. In order to randomize participants into groups, GraphPad software was employed to assign participants to the various groups (GraphPad Prism 5, GraphPad Software Inc, La Jolla, CA, USA). Each participant, on

entrance into the study, was sequentially assigned a number, thus being assigned to a group depending on the assignment of the software. Participants assigned to the IHG training group were instructed on the proper IHG exercise techniques.

After participants were assigned to their experimental group, they underwent 2 days of baseline testing procedures (pre-training), which were repeated by all participants after 4 weeks of IHG training or ABP monitoring (week 5; mid-training) and after 8 weeks of IHG training or ABP monitoring (post-training).

2.2 Isometric Handgrip Training

2.2.1 General Description

The IHG device (ZonaPLUS, Zona HEALTH, Boise, ID, USA; see Figure 6) is a computerized handgrip dynamometer programmed to execute 4 sets of 2-minute isometric contractions (using alternate hands) at 30% maximal voluntary contraction (MVC; determined at the onset of each exercise session, on each limb, via electronic linear load cells contained within each IHG device), each separated by 1-minute rest intervals (8,10).

Figure 6- Zona handgrip dynamometer

Participants trained in the seated position with their training arm (which alternated with each contraction) placed on a table directly in front of them. Their lower arm rested on the table at a 90° angle from the upper arm. See figure 7 for a picture of the IHG training position.

Figure 7- IHG training position

2.2.2 Exercise Training Protocol

Participants assigned to the IHG training group trained 3 times per week, for a total of 8 weeks. Two training sessions per week took place under the direct supervision of an exercise trainer, and the third session was conducted in the participants' home. Participants were provided with detailed instructions to ensure proper at home training, and were instructed to record their exercise, nutritional, and medication data in exercise log books to ensure consistency throughout the intervention period (Appendix H).

Each training session took approximately 30 minutes. Prior to the on-site training session, participants had their ABP measured using brachial arterial osciollometry (Dinamap ProCare 100, Critikon, Tampa, FL, USA). Participants then performed a bout of IHG exercise.

ABP Control Group

Participants randomized to the non-exercising control group visited the laboratory 2 times per week to have their ABP measured. In addition, this enabled acute monitoring of exercise, nutritional, and medication status throughout the study.

2.3 Outcome Measures

2.3.1 Testing Protocol Procedures

To minimize the influence of external factors on the cardiovascular measures, participants were asked to refrain from the consumption of alcohol and exercise for 24 hours prior to each testing session, and to avoid caffeine consumption for 12 hours prior (10). All testing was conducted in the morning, in a quiet, temperature-controlled room, following a light breakfast. On both testing days, all participants were asked to void their bladder prior to the testing session to minimize the effects of bladder distension on blood pressure (4).

2.3.2 Brachial Artery Osciollometry

Brachial artery osciollometry was used to measure pre- and post-IHG ABP and HR (Chapter 3: Acute effects of IHG exercise on arterial blood pressure and heart rate variability in medicated hypertensives and the influence of training), and for resting ABP and HR and 24-hour ambulatory ABP (Chapter 4: Effects of isometric handgrip training on resting and 24-hour ambulatory arterial blood pressure and heart rate variability in individuals medicated for hypertension).

Pre-IHG, post-IHG ABP and HR (immediately following, 1 hour and 2 hours post-IHG), and resting ABP and HR were measured (Dinamap ProCare 100, Critikon, Tampa, FL, USA) after 10 minutes of seated rest, whereby participants were instructed to keep their feet flat on the floor (12). Their right arm was adjusted adjacent to the body at heart

level and an ABP cuff (23 – 33 cm) was placed around the upper arm to acquire ABP.

Figure 8 shows the resting ABP upper-body and arm position.

Figure 8- Resting ABP body position

Three hour to 22 hour post-IHG ABPs and HRs were measured using an ambulatory osciollometric ABP monitoring device (Spacelabs 90207 Ambulatory Blood Pressure Monitor, SpaceLabs Inc., Redmond, WA, USA; Chapter 3: Acute and chronic effects of IHG exercise and training on post-exercise hypotension and heart rate variability in medicated hypertensives). Specifically, the upper right arm was secured with the ABP cuff (cuff size: 24 - 32 cm) and the square monitor was attached with a belt to the participant's waist (see Figure 8 for a depiction of monitor placement). This enabled an additional 20 hours of ABP and HR to be monitored post-IHG exercise (3 to 22 hours post-IHG), for a comprehensive total of 22 hours post-IHG (11). Finally, 24-hour ambulatory ABP and HR were assessed via the same oscillometric ambulatory ABP device (Chapter 4: Effects of isometric handgrip training on resting and 24-hour ambulatory arterial blood pressure and heart rate variability in individuals medicated for hypertension).

Figure 9- Spacelabs ambulatory ABP cuff: Depicts the placement of the ambulatory ABP cuff on the participant's right arm. The square monitor was secured on the participant's belt loop.

2.3.3 Electorcardiography

Electrocardiography was used to monitor continuous beat-to-beat heart rate (HR) (Chapter 3: Acute effects of IHG exercise on arterial blood pressure and heart rate variability in medicated hypertensives and the influence of training). Prior to and following an acute bout of IHG exercise, HR was measured pre-IHG using standard electrocardiography (ECG), whereby a set of 3 electrodes was placed on the participants' chest. To minimize lead placement errors, the same investigator performed the ECG setup at all testing sessions (3). All R-R interval HR data was recorded for 10 minutes for later analysis of HRV.

2.4 Data Analysis

2.4.1 Resting ABP and HR

For resting ABP, pre-IHG and post-IHG (immediately, 1-hour and 2 hours post-IHG) ABP and HR measures (Dinamap ProCare 100, Critikon, Tampa, FL, USA), 4 ABP and HR values were acquired by the same trained investigator following a 10-minute rest period, where each measure was separated by 2 minutes (14). The latter 3 measures were averaged and used in the final analysis.

2.4.2 Ambulatory ABP and HR

Twenty hour ambulatory and post-IHG ABP and HR (3 hours to 22 hours post-IHG; Spacelabs 90207 Ambulatory Blood Pressure Monitor, SpaceLabs Inc., Redmond, WA, USA) were recorded 2 times per hour during daytime hours (6 am – 10 pm), and 1 time per hour during nighttime hours (10 pm – 6 am) (7). Values were averaged during each hour, time period (daytime and nighttime), and during the entire 24-hour ambulatory period.

2.4.3 Pre- and Post-IHG HR for HRV analysis

As mentioned above in the section entitled: Electrocardiography, 10 minutes of R-R interval HR data was recorded prior to and following a bout of IHG for later analysis of pre- and post-IHG HRV. HR signal output was sampled at a frequency of 1,000 Hz. The analogue signals were converted to digital signals using a data acquisition board (PowerLab 8/30, ADInstruments Inc., Colorado Springs, CO, USA) for off-line beat-to-beat analysis. Ensemble averages of 256 beat sequences were taken from a minimum time series of 400 beats (9). Ectopic beats were edited and replaced via linear interpolation from adjacent cardiac cycles (9). Only tracings with ≤5% ectopy-corrected beats were accepted for analysis (9), therefore 2 of the 20 participants were excluded from the HRV analysis. To determine HRV, R-R (i.e. pulse) intervals obtained during the

baseline 10-minute data acquisition period were submitted to coarse graining spectral analysis (CGSA)(9,15).

CGSA is a non-invasive frequency domain analysis method used to estimate contributions of the PNS and SNS to short- and long-term oscillations in HR. The output of the CGSA analysis defines the following frequency bands: very low frequency (VLF), low frequency (LF), and high frequency (HF) (2). The VLF component corresponds to non-harmonic noise within the spectrum (13). The LF component provides insight into sympathetic modulation of HR, while the HF component provides insight into vagal HR modulation (1, 13). The ratio of LF:HF, although controversial, is said to provide insight into the sympathovagal influences contributing to the alterations in HR by the autonomic nervous system (13). The ratio of HF:TP provides information regarding the parasympathetic modulation of HR (9). CGSA allows for more accurate quantitative analysis of HRV by acquiring clearer peaks in the LF and HF components of the power spectrum (15). This type of analysis is particularly useful in clinical populations who have reduced harmonic spectral power and preserved non-harmonic power, such as those with hypertension (5).

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CHAPTER 3: Acute effects of IHG exercise on arterial blood pressure and heart rate variability in medicated hypertensives and the influence of training

(To be submitted to: Medicine and Science in Sport and Exercise)

Introduction:

Hypertension (HT), a disease characterized by sustained elevations in resting arterial blood pressure (ABP) and autonomic dysfunction (40), afflicts approximately 972 million people worldwide (11). Considerable attention has been given to the beneficial effects of aerobic and resistance exercise on reducing resting ABP in individuals with HT (7,12,15,35,36,41). Meta-analyses of aerobic training studies suggest average reductions of ~7 and ~6 mmHg in SBP and DBP, respectively (36), and average reductions of ~3 and ~4 mmHg in SBP and DBP, respectively, following resistance-training interventions (18) in this population. Based on the weight of the evidence, current guidelines put forth by the American College of Sports Medicine for individuals with hypertension recommend aerobic exercise (moderate-intensity for 30 - 60minutes) most days of the week and resistance exercise (1 set of 8 to 12 repetitions for the major muscle groups) 2 - 3 days per week (1). The mechanisms thought responsible for training-induced hypotension include vascular, structural, functional and neural changes that alter ABP by primarily inducing changes in total peripheral resistance (TPR; 36).

With respect to acute exercise, post-exercise hypotension (PEH), a phenomenon defined by a prolonged reduction in ABP following an acute bout of exercise, has been observed for up to 22 hours post-exercise and is most pronounced in those with hypertension (36). These acute exercise-induced changes in ABP not only offer the potential benefit of short-term ABP control by providing temporary reductions in daily ABP, but also offer insight into the pathophysiology of HT and the subsequent response to different modes of exercise.

PEH has predominantly been investigated following bouts of aerobic exercise, and has been observed following 10 to 170 minutes of a variety of aerobic exercises (walking, running, cycling; 19). The average short-term PEH reductions in resting ABP

are ~10/~7 mmHg, in SBP and DBP respectively (20). Although there is evidence to suggest that resistance exercise elicits a PEH response, this finding is not without controversy (8,20). For example, some studies have shown a prolonged (>2hrs) reduction in SBP, but no prolonged reduction in DBP (21,24), while others have found no post-exercise ABP alterations (33). Furthermore, some believe that the observed reductions in ABP post-resistance exercise may simply be due to the reperfusion of blood to the working muscles that were previously occluded during muscle contraction (20). Consensus in the literature suggests that the mechanisms responsible for PEH are likely multi-faceted, and include a reduction in vascular resistance and/or decreases in sympathetic nerve activity (5,9,12,17,20,34).

A more novel form of exercise training, isometric handgrip (IHG) training (four, 2-minute sustained contractions at 30% maximal voluntary contraction (MVC), separated by a timed rest period, 3x/week for 8 - 10 weeks) is a less time consuming exercise repeatedly shown to reduce resting ABP (19,26,27,38). Recently, a meta-analysis supported bilateral IHG training as an efficacious way to attain significant exercise-induced ABP reductions (~5 and ~3 mmHg in SBP and DBP, respectively) in non-clinical (young healthy individuals) and clinical populations (hypertension) (19). Although the acute effects of IHG on post-IHG ABP in individuals with hypertension have not been thoroughly investigated, in a population of 18 older (70 ± 5 years) healthy adults (9 females), a post-IHG reduction of ~3 mmHg in SBP was observed 5 minutes post-IHG (30).

In addition to the ABP-specific effects of acute and/or chronic aerobic, resistance and isometric exercise, the broader scale effects of exercise on autonomic function have been examined. Spectral analysis of heart rate variability (HRV) is a popular non-invasive tool used to assess autonomic function, and provides insight into the autonomic

modulation of heart rate (HR) (40). HRV assessment has been widely employed under resting conditions, and following acute and chronic exercise, in both non-clinical and clinical populations, including those hypertensive individuals with compromised nervous systems. Coarse graining spectral analysis (CGSA) is a non-invasive frequency domain analysis method used to estimate contributions of the parasympathetic and sympathetic nervous systems to short- and long-term oscillations in HR. CGSA yields two components, harmonic and non-harmonic components, with the latter representing fractal noise. The harmonic portion of the spectrum can further be subdivided into 3 main power components: very low frequency (VLF; harmonic noise), low frequency (LF; primarily represents sympathetic neural oscillations of HR), and high frequency (HF; indicative of vagal modulation of HR; 2). Total power (TP) represents the complete power of the harmonic spectrum (2). The ratio of LF:HF, although controversial, is said to provide insight into the sympathovagal influences contributing to the alterations in HR by the autonomic nervous system (40). The ratio of HF: TP provides information regarding the parasympathetic modulation of HR (27). CGSA allows for more accurate quantitative analysis of HRV by acquiring clearer peaks in the LF and HF components of the power spectrum (42). This type of analysis is particularly useful in clinical populations who have reduced harmonic spectral power and preserved non-harmonic or fractal power, such as those with hypertension (32).

The effects of acute exercise on HRV have been under-investigated and the available data provides evidence both for and against acute changes in HR modulation immediately following an exercise bout. For example, with respect to aerobic exercise, Javorka and colleagues (16) observed increased HF power and decreased LF power following an acute bout (12 minutes) of bench step climbs in 17 healthy normotensive males (20 ± 0.2 years) (16). The authors attributed these findings to an increase in

parasympathetic tone upon the cessation of exercise. Similarly, the findings of Raczak et al. (38), who investigated the effects of 30 minutes of constant treadmill exercise on post-exercise HRV in 18 healthy men (20 - 24 years old), support augmented parasympathetic activity following aerobic exercise (38). In contrast, other studies have shown decreases in post-exercise HRV. A population of 10 healthy, normotensive, sedentary men (24.6 ± 0.6 years) who engaged in both interval (45 minutes) and steady state (time adjusted so participants produced the same amount of work as interval exercise) cycling exercise, on separate occasions, exhibited decreases in spectral indices of autonomic function (LF, HF, TP; 31). In accordance with these findings, 13 masters athletes (men and women; regular cyclers; 52.1 ± 3.3 years) who engaged in 25 - 35 minutes of incremental cycling until a lactate threshold of 4.5 mmol was observed, showed post-exercise decreases in indices of sympathetic, parasympathetic, and total autonomic nervous system function (TP, VLF, LF and HF; 4).

Few studies have investigated the acute autonomic responses to resistance exercise, yet like aerobic exercise, the findings are somewhat equivocal. Rezk and colleagues (39) investigated the effects of whole body resistance exercise (3 sets of 20 repetitions) on acute HRV in 17 healthy men (n = 8) and women (n = 9) (~23 years old), and observed increases in LF, reductions in HF, and no change in TP (39). In contrast, Heffernan and colleagues (14) investigated the effect of whole body resistance exercise (3 sets of 10 repetitions) on acute HRV in 14 healthy young men (21 - 29 years old), and observed reductions in TP, LF, and HF (14).

To our knowledge, only one study has investigated the acute effects of a bout of IHG on HRV. Millar and colleagues (30) recently found that an acute bout of bilateral IHG (4, 30% MVC contractions, sustained for 2-minutes with alternate hands, separated by a 1-minute rest period) improves vagal modulation of HR in 18 healthy, older (70 ± 5

years) individuals (females = 9). As this study was performed in normotensive individuals, further investigation of the effects of acute IHG on HRV in individuals with hypertension is needed.

Currently, there are no studies investigating the effects of exercise training on the acute HRV responses to a bout of aerobic, resistance or isometric exercise.

The present study was designed to address the following research questions: 1) Does an acute bout of IHG cause *sustained* reductions in ABP (PEH) and improvements in vagal modulation of HR in individuals with HT? and, 2) Does 8-weeks of IHG training alter these responses? We hypothesized that an acute bout of IHG would elicit a PEH response and improve vagal modulation. We further hypothesized that we would see an attenuated post-training PEH response, as PEH has been attributed to alterations in autonomic function, we also expected that post-IHG increases in vagal modulation of HR (30) would be attenuated with training.

Participants and Methods:

Participants. Twenty-five hypertensives, all of who were receiving pharmacotherapy to treat their hypertension and who had been medicated for at least 4 months, participated in this investigation. Five participants voluntarily withdrew from the investigation (2 in IHG training group, 3 in the control group), as time commitments interfered with study participation. Participants were excluded if they had diabetes, a paced heart rhythm at rest, frequent ventricular premature heartbeats, heart failure, or if they had any physical limitation that would have prevented them from performing IHG exercise. Vasoactive medications, external exercise sessions, and nutritional status remained unchanged throughout the investigation. Participant characteristics are presented in Table 1. The Research Ethics Board of the University of Windsor approved the investigation, and all participants provided written, informed consent.

Table 1: Baseline characteristics of participants

Participants	All (N = 25)	Training Group (n = 11)	Control Group (n = 9)
Females (n)	13	4	6
Age (years)	61 ± 8.2	60.0 ± 8.5	62.7 ± 6.1
BMI (kg/m^2)	30.8 ± 7.2	31.7 ± 7.5	31.0 ± 8.8
Systolic Blood Pressure (SBP; mmHg)	114.6 ± 11.3	113.9 ± 12.7	117.8 ± 14.3
Diastolic Blood Pressure (DBP; mmHg)	67.5 ± 10.3	60.7 ± 11.6	67.5 ± 4.2
Heart Rate (beats/min)	66.9 ± 10.8	62.8 ± 8.5	69.5 ± 15.3
Medication: (n)			
Diuretic	2	2	1
Angiotensin Converting Enzyme (ACE)	3	1	1
Aldosterone Receptor Blocker (ARB)	3	1	1
Calcium Channel Blocker (CCB)	3	2	0
Diuretic + ACE	1	1	0
Diuretic + ARB	3	1	1
ACE + Beta Blocker (BB)	3	1	1
ARB + CCB	1	0	1
ARB + BB	1	1	0
Diuretic + ACE + BB	2	1	1
Diuretic + ARB + BB	1	0	1
Diuretic + ARB + CCB	1	0	0
Diuretic + ARB + CCB + BB	1	1	0

Values are mean ± S.D.

All participants completed a medical questionnaire, and were habituated to the testing procedures. Following habituation, participants were randomized to an IHG training group or a non-exercising control group (GraphPad Prism 5, GraphPad Software Inc, La Jolla, CA, USA). Participants assigned to the IHG training group were instructed on the proper IHG exercise techniques.

Study design*.* This investigation employed a between-subject repeated

measures design. ABP and HRV were measured prior to and following a bout of IHG exercise (4 sets of 2-minute isometric contractions (using alternate hands) on a programmed handgrip dynamometer (ZonaPLUS, Zona HEALTH, Boise, ID, USA) at 30% MVC, each separated by 1-minute rest intervals (26,27,29), and were assessed at baseline, and after 4- and 8- weeks of IHG training (or no training for the control group).

Exercise training protocol. Participants assigned to the IHG training group trained 3 times per week for 8 weeks using the above-described IHG protocol. Two training sessions per week took place under the direct supervision of an exercise trainer, and the third session was conducted in the participants' home. Participants were provided with detailed IHG instructions to ensure proper at home training. To establish similar face time with study investigators, participants randomized to the non-exercising control group visited the laboratory 2 times per week to have their resting ABP measured (29).

Testing protocol. All data was acquired while participants were seated with their right arm adjusted adjacent to the body at heart level and their feet flat on the floor (37). All IHG bouts were performed with the participant in the seated position with their training arm (which alternated with each contractions) placed on a table directly in front of them. Their lower arm rested on the table at a 90° angle from the upper arm. All testing was conducted in the morning, in a quiet, temperature-controlled room, following a light breakfast, a 24-hour abstinence from alcohol and exercise and a 12-hour abstinence from caffeine (27). Participants were asked to void their bladder prior to all testing session to minimize the effects of bladder distension on blood pressure (7).

A schematic of the testing protocol is depicted in Figure 10. In brief, prior to an acute bout of IHG exercise (4 sets of 2-minute bilateral isometric contractions at 30% MVC, each separated by a 1 minute rest period; ZonaPLUS, Zona HEALTH, Boise, ID,

USA) (26,27,40), pre-ABP and HR were measured in the right arm using brachial artery oscillometry (Dinamap ProCare 100, Critikon, Tampa, FL, USA; cuff 23–33 cm) after 10 minutes of seated rest (37). R-R interval HR data was recorded for 10 minutes for later analysis of pre-IHG HRV. R-R intervals were acquired using standard electrocardiography (ECG), whereby a set of 3 electrodes was placed on the participants' chest. To minimize lead placement errors, the same investigator performed the ECG setup at all testing sessions (3). Following this data collection period, participants performed an acute bout of IHG exercise. Immediately following the last rest interval, HR was recorded for 10 minutes for later assessment of post-IHG HRV, and ABP and HR were re-assessed. ABP and HR were evaluated after 1 hour and 2 hours post-exercise in the laboratory setting (Dinamap ProCare 100, Critikon, Tampa, FL, USA; 21). Following the final in-house ABP assessment, an additional 20-hours of post-IHG ABP and HR were acquired (Spacelabs 90207 Ambulatory Blood Pressure Monitor, SpaceLabs Inc., Redmond, WA, USA) to allow for a comprehensive 22 hour post-exercise evaluation of ABP and HR period to be captured (post-IHG ambulatory ABP and HR; 36).

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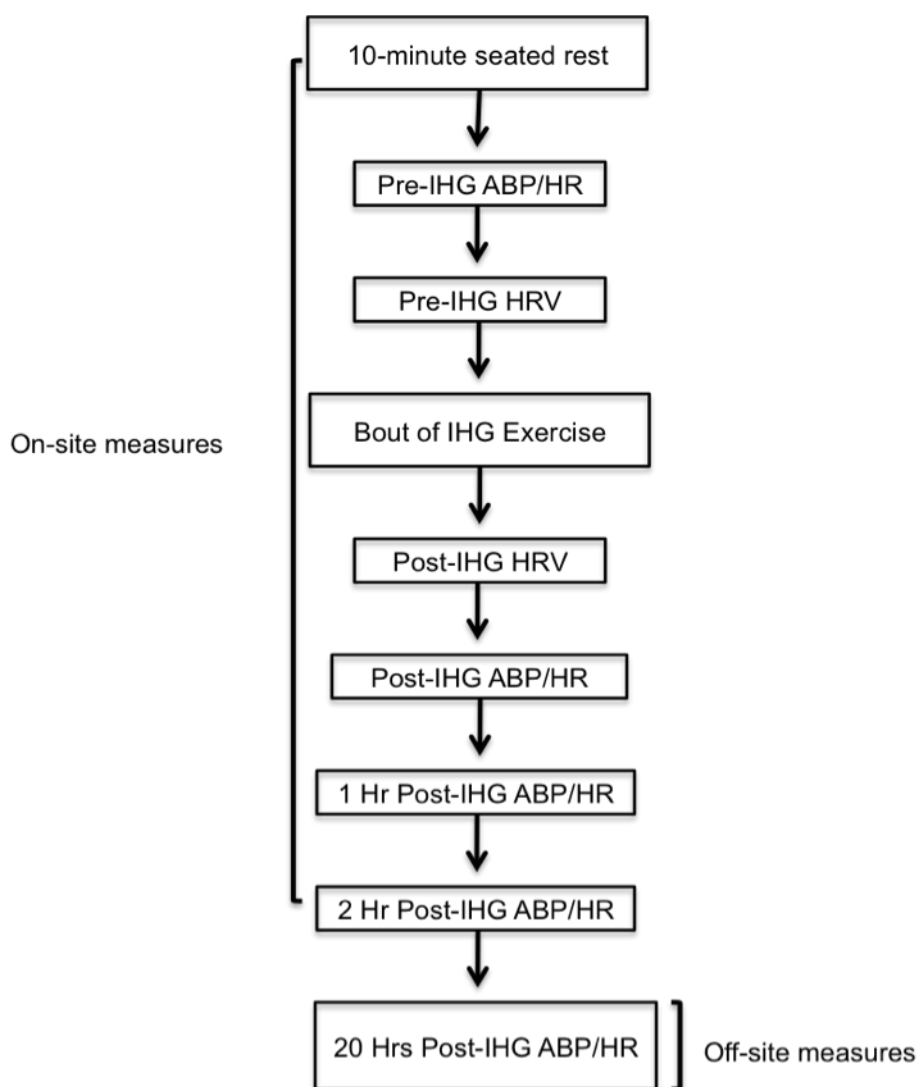
Figure 10- Testing protocol schematic

Data Analysis:

Pre-IHG ABP and HR and on-site post-IHG ABP and HR (immediately, 1 hour, and 2 hours post-IHG): Four pre-IHG ABP and HR values were acquired, each separated by 2 minutes (Dinamap ProCare 100, Critikon, Tampa, FL, USA) by the same trained investigator following a 10-minute rest period (42). The latter 3 measures were

averaged and used in the final analysis (42). Following a bout of IHG exercise, ABP and HR were again acquired, using the same technique previously described.

Off-site post-IHG ABP and HR: Post-IHG ABPs and HRs were recorded 2 times per hour during daytime hours (6 am – 10 pm), and 1 time per hour during nighttime hours (10 pm – 6 am) over the time period spanning 3 hours to 22 hours post-IHG exercise using an ambulatory brachial artery oscillometric device (Spacelabs 90207 Ambulatory Blood Pressure Monitor, SpaceLabs Inc., Redmond, WA, USA) (22). Values were averaged during each hour, during each time period (daytime and nighttime), and during the entire 20-hour ambulatory period.

Pre- and Post-IHG HRV analysis: Beat-to-beat HR was acquired pre- and post-IHG using standard electrocardiography (ECG), as previously described (3). HR signal output was sampled at a frequency of 1,000 Hz. The analogue signals were converted to digital signals using a data acquisition board (PowerLab 8/30, ADInstruments Inc., Colorado Springs, CO, USA) for off-line beat-to-beat analysis. Ensemble averages of 256 beat sequences were taken from a minimum time series of 400 beats (28). Ectopic beats were edited and replaced via linear interpolation from adjacent cardiac cycles (28). Only tracings with ≤5% ectopy-corrected beats were accepted for analysis (28), thus 2 of the 20 participants (both of whom were in the training group) were excluded from the HRV analysis. To assess HRV, these R-R (i.e. pulse) intervals were then submitted to CGSA (28,43).

Statistical Analysis:

One-way ANOVAs (group) of baseline pre-IHG ABP, pre-IHG HR and pre-IHG HRV were employed to determine if baseline differences existed between the training and control groups at baseline. As no differences were revealed (P ≥ 0.05), two-way ANOVAs (group x phase) with repeated measures (time) were used to analyze pre-IHG

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to post-IHG alterations in ABP (SBP and DBP), HR and HRV (VLF, LF, HF, TP, LF:HF ratio, HF:TP ratio). Where applicable, post-hoc analyses were conducted using paired-sample t-tests, which used Bonferroni corrected alpha levels.

All data was re-assessed after separately controlling for, as between subject factors, gender (male or female), medication (single or multiple medications) and baseline ABP (controlled to within the normal range (≤120/80 mmHg) or uncontrolled (≥120/80 mmHg)).

Statistical significance was set at $P \le 0.05$. Analysis of data was completed using IBM (PASW) SPSS Statistics 18 (SPSS Inc., Chicago, IL, USA).

Results:

Acute cardiovascular effects of IHG exercise

Immediately following a bout of IHG exercise, analyses of variance revealed no significant differences in SBP or DBP pre- to post-IHG (all $P \ge 0.05$) in either the IHG training (Pre-IHG: 118 ± 14 and 67± 4 mmHg to Post: 117 ± 13 and 70 ± 6 mmHg in SBP and DBP, respectively), or control group (Pre-IHG: 114 ± 13 and 61 ± 12 mmHg, Post-IHG: 114 ± 10 and 62 ± 10 mmHg in SBP and DBP, respectively).

In both groups, SBP was significantly elevated above pre-IHG levels from 2 - 7 hours following acute IHG (Training: 126 ± 16 mmHg, 134 ± 11 mmHg, 133 ± 17 mmHg, 132 ± 11 mmHg, 132 ± 12 mmHg, and 133 ± 16 mmHg, respectively; Control: 126 ± 14 mmHg, 141 ± 13 mmHg, 139 ± 14 mmHg, 131 ± 13 mmHg, 129 ± 14 mmHg, and 126 ± 19 mmHg, respectively) and again from 18 - 22 hours post-IHG (Training: 122 ± 10 mmHg, 130 ± 10 mmHg, 127 ± 14 mmHg, 124 ± 14 mmHg, and 124 ± 14 mmHg, respectively; Control: 133 ± 18 mmHg, 135 ± 19 mmHg, 135 ± 23 mmHg, 133 ± 20 mmHg, and 131 ± 18 mmHg, respectively) (all $P \le 0.005$; Figure 11).

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Figure 11: The 22-hour SBP response to acute IHG exercise. Hour 0 denotes pre-IHG SBP value. * Significantly different from pre-IHG values. $P \leq 0.005$; N = 20.

From 1 - 8 hours following IHG exercise, DBP remained significantly elevated above pre-IHG DBP values ($P \leq 0.003$) in both groups (Training: 72 ± 5 mmHg, 76 ± 10 mmHg, 78 ± 10 mmHg, 78 ± 14 mmHg, 79 ± 10 mmHg, 80 ± 11 mmHg, 80 ± 11 mmHg, and 79 ± 13 mmHg, respectively; Control: 63 ± 9 mmHg, 66 ± 9 mmHg, 84 ± 12 mmHg, 76 ± 12 mmHg, 72 ± 11 mmHg, 70 ± 7 mmHg, 71 ± 9 mmHg, and 66 ± 9 mmHg, respectively). At 19 - 22 hours post-IHG, there was a significant increase in DBP when compared to pre-IHG DBPs (Training: 77 ± 13 mmHg, 75 ± 14 mmHg, 76 ± 15 mmHg, and 77 ± 10 mmHg, respectively; Control: 76 ± 18 mmHg, 77 ± 15 mmHg, 79 ± 13 mmHg, and 76 ± 16 mmHg, respectively; $P \leq 0.001$). The 22-hour post-IHG SBP and DBP responses are shown in Figures 11 and 12, respectively.
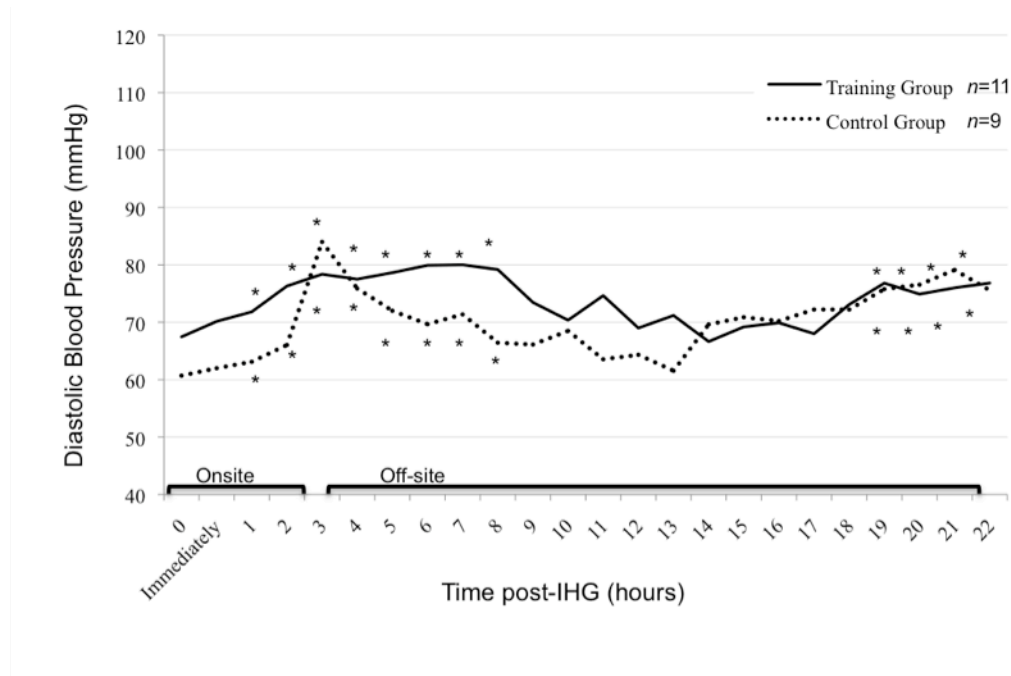
Figure 12: The 22-hour DBP response to acute IHG exercise. Hour 0 denotes pre-IHG DBP value. * Significantly different from pre-IHG values. $P \leq 0.003$; N = 20.

HR was significantly reduced immediately post-IHG compared to pre-IHG HR (P < 0.001) in both the training (Pre-IHG: 69 ± 17beats/min to Post-IHG: 66 ± 15beats/min and control groups (Pre-IHG: 63 ± 9beats/min to Post-IHG: 60 ± 9beats/min). Post-IHG HR remained significantly lower than pre-IHG values for 2 hours following the IHG exercise (Training: 63 ± 12beats/min, and 64 ± 16beats/min; Control: 59 ± 9beats/min, 59±11beats/min; P < 0.001). HR returned to pre-IHG levels for the remainder of the test period (3 - 22 hours post-IHG; all $P \geq 0.005$). The 22-hour post-IHG HR responses are shown in Figure 13.

All data was re-assessed after separately controlling for gender, medication, and baseline ABP, and no significant effects were revealed (all $P \geq 0.05$).
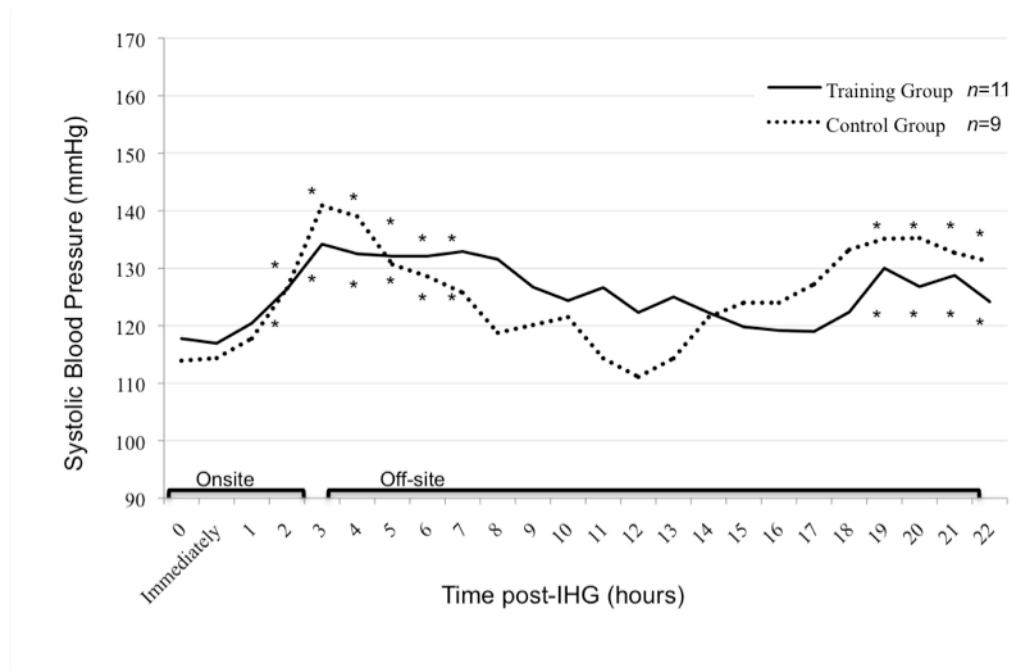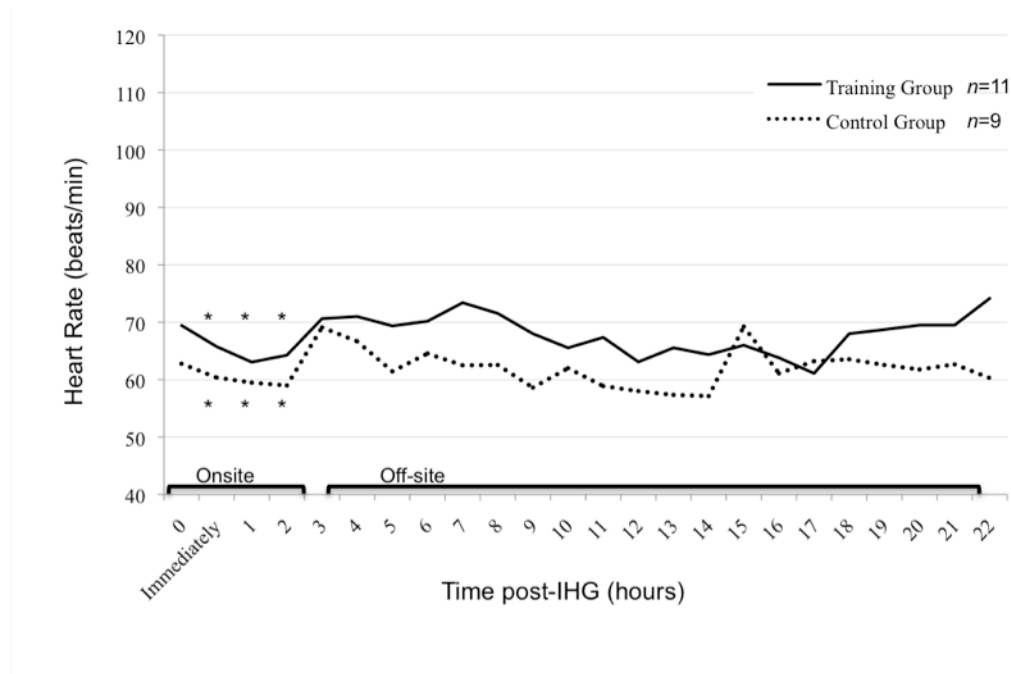
Figure 13: The 22-hour HR response to acute IHG exercise. Hour 0 denotes the pre-IHG HR value. * Significantly different from pre-IHG values. $P < 0.001$, N = 20.

Following an acute bout of IHG exercise, analyses of variance of the harmonic components of HRV (VLF, LF, HF, TP, LF/HF, and HF/TP) revealed no significant effects (all $P \geq 0.3$) (Table 2).

Effects of IHG training on acute cardiovascular responses

Acute ABP and HR responses to IHG were measured following both 4- and 8-weeks of IHG training (or no-training for the control group). After 4-weeks of IHG training, the SBP response to IHG in both groups was similar to baseline measures. Immediately following IHG exercise, SBP remained unchanged from pre-IHG SBP values ($P = 0.3$). From 1 - 7 hours and 16 - 22 hours post-IHG, SBP was significantly elevated compared to pre-IHG SBP values ($P \leq 0.002$). Following 8-weeks of IHG training, the SBP response to IHG exercise remained similar to the responses observed at baseline and 4-weeks post-training. Again, SBP remained unchanged from pre-IHG values immediately

following an acute bout of IHG, yet it was significantly elevated above pre-IHG values from 1 - 7 hours and 17 - 20 hours post-IHG ($P \leq 0.002$).

Following 4-weeks of IHG training (or no-training for the control group), post-IHG DBP did not significantly change from pre-IHG DBP values ($P = 0.1$) in either group. Similar to pre-training, from 1 to 7, 15 to 17, and 19 hours post-IHG, there was a significant increase in DBP, as compared to pre-IHG DBP values ($P \leq 0.005$). Following 8-weeks of IHG training (or no-training for the control group), DBP immediately following IHG was significantly increased when compared to pre-IHG DBP values ($P = 0.003$). During the first hour post-IHG, DBP returned to pre-IHG values. However, DBP again increased significantly from pre-IHG levels from 2 - 7 and 18 - 20 hours post-IHG (all $P \leq 0.002$).

Similar to pre-training, HR was significantly reduced following a bout of IHG exercise ($P = 0.002$) in both training and control group following 4-weeks of IHG training. The reduction in HR was only observed immediately following the IHG bout, as 1 - 22 hour post-IHG HR remained unchanged from pre-IHG HR values ($P \geq 0.005$). Post-training there were no significant changes in HR, following an acute bout of IHG for either group, at any time point.

Two-way ANOVAs of mean 24-hour ambulatory ABP and HR, nighttime ABP and HR, and daytime ABP and HR revealed no significant main effects or interactions ($P \geq 0.6$) (Data not presented).

With respect to HRV, significant differences in pre- to post-IHG VLF, LF, HF, TP, LF:HF ratio, or HF:TP ratio were not observed ($P \geq 0.05$) in the training group following 4- or 8-weeks of IHG training, when compared to the non-exercising control group. For HF power, however, there was a significant interaction between group and phase ($P = 0.05$) (Table 2), yet post-hoc analysis revealed no significant difference between pre-

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and post-IHG alterations in HF power at baseline, after 4-weeks of training, or after 8-weeks of training (all $P \geq 0.07$).

Table 2: HRV indices pre- and post-IHG at baseline, after 4- and 8- weeks of training

	Baseline		After 4-weeks of IHG training		After 8-weeks of IHG training	
	Pre-IHG	Post-IHG	Pre-IHG	Post-IHG	Pre-IHG	Post-IHG
VLF (ms^2)						
Training	203.7 ± 275.0	295.3 ± 547.9	99.2 ± 86.0	110.7 ± 83.1	113.0 ± 132.0	75.7 ± 52.3
Control	158.0 ± 122.7	64.6 ± 71.2	99.4 ± 86.2	59.8 ± 45.9	98.6 ± 107.7	101.2 ± 100.9
LF (ms^2)						
Training	86.9 ± 144.1	120.1 ± 193.4	50.7 ± 33.6	64.2 ± 77.4	47.7 ± 48.3	40.0 ± 30.7
Control	108.2 ± 120.6	53.4 ± 77.4	76.2 ± 64.3	82.7 ± 123.8	47.7 ± 61.3	103.9 ± 135.6
HF (ms^2)						
Training	65.0 ± 103.6	64.8 ± 92.1	102.7 ± 119.6	106.2 ± 132.8	83.8 ± 109.1	165.1 ± 240.1
Control	93.0±124.0	45.3 ± 48.8	41.5 ± 33.2	28.2 ± 24.9	73.1 ± 91.5	109.1 ± 112.8
TP (ms^2)						
Training	355.6 ± 486.7	480.2 ± 766.2	252.7 ± 211.8	281.1 ± 213.0	244.4 ± 252.6	280.9 ± 266.7
Control	359.2 ± 323.7	163.3 ± 140.3	217.1 ± 124.1	170.7 ± 143.6	219.4 ± 172.9	314.1 ± 245.0
LF/HF (ms^2)						
Training	2.1 ± 2.1	5.1 ± 6.9	0.8 ± 0.8	0.9 ± 0.6	3.2 ± 5.6	2.0 ± 4.3
Control	3.1 ± 6.1	3.7 ± 8.1	3.8 ± 4.9	7.9 ± 15.7	1.6 ± 2.5	1.4 ± 1.5
HF/TP (ms^2)						
Training	0.3 ± 0.2	0.4 ± 0.3	0.4 ± 0.2	0.4 ± 0.2	0.4 ± 0.3	0.4 ± 0.2
Control	0.2 ± 0.1	0.4 ± 0.4	0.2 ± 0.2	0.3 ± 0.3	0.3 ± 0.3	0.4 ± 0.3

Values are mean ± S.D. N = 20 (training group: n = 9; control group: n = 9).

Discussion:

In healthy individuals, an acute bout of IHG elicits an immediate reduction in post-exercise ABP and an improvement in vagal HR modulation (30). Unknown was whether: 1) this ABP reduction is *sustained* (PEH), a finding which would be of great benefit to individuals with elevated resting ABP (HT), 2) acute post-IHG increases in vagal modulation also occur in hypertensives, a population with compromised autonomic

function, and/or 3) these collective responses change with chronic exposure to the IHG stimulus. The purpose of this investigation was to address the hypotheses that an acute bout of IHG would cause *sustained* reductions in ABP (PEH) and improve vagal modulation of HR in individuals with HT and that 8-weeks of IHG training would attenuate these post-IHG responses. Three prominent and novel findings emerged from this study: in medicated hypertensives 1) an acute bout of IHG does not elicit a PEH response, 2) acute IHG exercise does cause post-exercise improvement in vagal modulation of HR, and 3) 8-weeks of IHG training does not alter these acute responses.

Acute cardiovascular effects of IHG exercise

Contrary to our hypothesis, an acute bout of IHG exercise did not elicit a PEH response. Although reductions in SBP (~3 mmHg) have been observed 5-minutes following IHG exercise in healthy older individuals, this did not translate to *sustained* ABP reductions (PEH) in our population of medicated hypertensives (30). In contrast, SBP and DBP were both elevated above pre-IHG values for the first 5 - 6 hours following IHG exercise, followed by increases in ABP from 15 - 21 hours post-exercise. We do not consider this rise to be concerning, however, as all post-IHG values remained within the normal ambulatory ABP range. The lack of a DBP response to an acute bout of IHG in this investigation, however, is in line with the findings of Millar and colleagues (30).

Why did we not see a *sustained* reduction in ABP (PEH) following IHG? The population in the current study was one of well-controlled medicated hypertensive individuals (mean resting ABP for the training group: ~114/61 mmHg and for the control group: ~118/68 mmHg) with well-balanced medication regimens between the two groups (Table 1), whereas the population in the study by Millar and colleagues (30) had higher initial ABP (mean resting ABP: 125/74 mmHg). These findings suggest that initial resting ABP may influence the acute hypotensive response to IHG exercise, just as it does with

aerobic exercise. Additionally, many mechanisms have been suggested to play a role in post-aerobic exercise PEH, one of which is a reduction in cardiac output. Following an acute bout of aerobic exercise, individuals with HT have sustained reductions in cardiac output (26), likely due to a reduction in blood volume, leading to a consequent reduction in stroke volume and ABP (as ABP is the product of cardiac output (stroke volume and heart rate) and total peripheral resistance (TPR; 20)). Acute resistance exercise also elicits post-exercise reductions in cardiac output, which again have been attributed to post-exercise reductions in stroke volume (39). Unlike aerobic and resistance exercises, IHG exercise may not provide a large enough stimulus or been an effective enough stimulus in our population of medicated hypertensives to evoke a reduction in blood volume (sustained or otherwise), leaving stroke volume and cardiac output unaltered and post-IHG ABP unchanged. Future work should investigate the effects of IHG exercise on blood volume, stroke volume and cardiac output alterations.

TPR itself is another mechanism thought to be responsible for the PEH response following aerobic exercise. Reductions in TPR have been observed in hypertensive individuals following an acute bout of aerobic exercise (27). As aerobic exercise is a dynamic exercise involving large muscle groups, local vasodilation in the vasculature of the large muscle masses could account for the ABP reduction post-exercise. IHG exercise, however, only uses the small muscles of the forearm. The stimulus from IHG exercise increases vasodilatory capacity and conductance, and lowers resistance in the forearm vasculature (26); however, these changes may not provide a large enough alteration, or be sustained for an extended period of time, to evoke systemic changes in TPR and evoke a PEH response post-IHG. Furthermore, it is generally accepted that following aerobic exercise there is a marked decrease in sympathetic nerve activity and an increase in parasympathetic activity (20), and this modulation has been attributed to

the PEH response (20, 30). The lack of reduction in sympathetic outflow (11), and the collective lack of alteration in autonomic function following IHG exercise in this study (discussed below) may also be responsible for the absent PEH response following IHG exercise in our population of medicated hypertensives.

The elevations as opposed to the anticipated reductions in post-exercise ABP may have occurred for a number of reasons, including acute anxiety, ambulatory activities, and early morning rises in ABP. As participants were required to remain in the laboratory for the first 2 hours post-exercise, ABP may have been influenced by the their anticipation of leaving the laboratory (33). This was evident by repeat questions of "is it time to go yet?" or "how much longer." With respect to the novel measures of post-exercise ABP using an ambulatory device, increases in SBP and DBP seen in the first 5 - 6 hours following the IHG exercise were likely due to the ambulatory activity of the participants. In an attempt to mimic activities of daily living in the general hypertensive population, activities following laboratory testing were not controlled. For example, many participants returned to work immediately following the study, which could explain the observed SBP and DBP increases. The increases in ABP seen from 15 - 21 hours post-exercise occurred during the waking times of the participants, 3 am – 9 am, associated with increases in ABP (13).

Unlike ABP, there was a significant reduction in HR immediately following IHG exercise (~3 beats/min). This finding is unlike the HR findings of Millar and colleagues (30), as no significant differences (increase or decrease) in HR following IHG exercise were observed. Increases in HR, with subsequent increases in cardiac output, have also been noted following aerobic exercise (20). The variation in HR responses to exercise may be attributed to the set point of the baroreflex and/or alterations in autonomic function following isometric exercise. As the participants in the current study experienced

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reductions in HR following exercise, with no alterations in autonomic function (HRV), the

HR reduction is most likely due to acute alterations in baroreflex sensitivity post-exercise

in effort to offset the rise in ABP (20). Alternatively, the reduction in HR observed

following IHG exercise might simply have been due to normal fluctuations in HR that fell

within the range of statistical significance.

Autonomic function was not altered by an acute bout of IHG in our study

population. This finding did not support our hypothesis that vagal modulation of HR

would be improved following a bout of IHG exercise. Again, these findings are in contrast

with the results observed by Millar and colleagues (30), who found marked increases in

parasympathetic activity following IHG exercise. As previously noted, all participants in

the current study were medicated for hypertension, some of whom were on medications

known to increase autonomic function. For example, beta-blockers (BBs) and

angiotensin converting enzyme inhibitors (ACE inhibitors) have been shown to not only

improve ABP, but also improve HRV after 1 month (20,21). As more than half of the

individuals in both our training group and the study population as a whole (Table 1) were

on one or a combination of these drugs, and had been medicated for at least 4 months

before beginning the study, the participants may have reached their capacity for maximal

autonomic improvements. As such, these medications may have contributed to the lack

of a post-IHG alteration in vagal modulation of HR.

Effects of IHG training on the acute cardiovascular responses

To date, there is no documentation of the effects of training on the PEH

response. In the current study, post-exercise increases in ABP remained unaltered with

4- and 8-weeks of IHG training. These findings suggest chronic exposure to the acute

IHG stimulus does not alter the physiological responses to IHG exercise nor does it

change the responses to align with our original hypothesis. Again, initial resting ABPs and medications likely played a role in the lack of change with training. Although normotensive individuals have shown small PEH responses, these findings are inconsistent (20). As individuals in this study had ABPs already within the normal range, the capacity for a PEH response, and therefore a change in this response, was limited. Remarkably, the acute response to the IHG stimulus was replicated almost identically after 4- and 8- weeks of training. This supports the theory that the individuals in this study were much like normotensive individuals, and as such, had a limited ability to alter their response to the IHG stimulus with training.

After 4-weeks of IHG training, post-IHG HR reductions were similar to those observed at baseline, however, after 8-weeks of IHG training, this response was no longer present. It is possible that testing-anxiety or alterations in breathing are responsible for this change in HR response to the IHG stimulus. Feeling of anxiety towards the testing session is unlikely, as participants had taken part in testing on prior occasions, however situational anxiety cannot be ruled out. Contrarily, the lack of a reduction in HR post-IHG following 8-weeks of training may simply be due to minute-to-minute fluctuations in HR.

IHG training did not alter the post-exercise autonomic response to an acute bout of IHG exercise, and thus did not support our hypothesis of an attenuated increase in vagal modulation of HR following acute IHG. As with the post-training acute ABP responses to the IHG stimulus, medications likely played a role in the lack of alterations in post-exercise HRV following training. As previously mentioned, participants may have experienced maximum benefits from medication, and therefore, had little to no room for improvement or changes in indices of HRV.

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Conclusions and Future Direction:

This investigation revealed the novel findings that an acute bout of IHG does not cause *sustained* reductions in ABP (PEH) nor does it improve vagal modulation of HR in a population of well-controlled medicated hypertensives, and these responses are unchanged with 8-weeks of IHG training. Future studies should investigate the acute and chronic effects of IHG on post-exercise ABP and HRV in individuals medicated for hypertension with resting ABP values above the normal range (> 120/80 mmHg), and/or in unmedicated hypertensives with resting ABP $\geq$ 140/90 mmHg.

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CHAPTER 4: Effects of isometric handgrip training on resting and 24-hour ambulatory arterial blood pressure and heart rate variability in individuals medicated for hypertension

(To be submitted to: Journal of Hypertension)

Introduction:

Hypertension (HT), a disease characterized by sustained elevations in resting arterial blood pressure (ABP) and autonomic dysfunction (35), is a prominent risk factor for the world's leading cause of death, cardiovascular disease (CVD; 28). It afflicts 1 in 3 Americans (28) and accounts for 77 billion dollars in health care spending in the United States (17). Aerobic exercise training (walking, running, and cycling, 1 to 7 days/week, for 30-60 minutes, at 30 to 90% maximum oxygen consumption) significantly reduces resting systolic ABP (SBP; ~7 mmHg) and diastolic ABP (DBP; ~6 mmHg) in individuals with HT (30). Resistance exercise training (1 set of 10 repetitions of all the major muscle groups, 2 - 3 times per week; 1) is recommended as an adjunct to aerobic exercise training, as the weight of the evidence also supports a reduction in resting ABP (~3 mmHg in both SBP and DBP) (14).

Though resting ABP provides general risk stratification for HT, ambulatory ABP is more efficacious in predicting CVD related events than clinical resting ABP measures (31). Aerobic exercise training (walking, running, or cycling, 1 to 7 days/week, for 15-63 minutes, at 30 to 88% heart rate reserve) has been shown to reduce ambulatory ABP (6). Meta-analyses of aerobic training and ambulatory ABP support reductions in daytime SBP and DBP of ~3 mmHg and ~2 mmHg, respectively, while nighttime ABP decreased by ~3 mmHg for both SBP and DBP. Although resistance exercise training and its effect on 24-hour ambulatory ABP has been investigated to a lesser extent, available evidence does not support post-training reductions in ambulatory ABP (6).

Isometric handgrip (IHG) training (4, 2-minute bilateral isometric contractions performed at 30% of maximal voluntary contraction and separated by a timed rest period, 3X/week for 8 -10 weeks) is a novel and less time consuming form of exercise training repeatedly shown to reduce resting ABP in small scale investigations in

individuals with and without HT (14,20,21,25). However, the effects of IHG training on ambulatory ABP are unknown. To date, no randomized controlled trials have examined the effects of IHG training on resting ABP concomitant with ambulatory ABP.

Spectral analysis of heart rate variability (HRV) is a popular non-invasive tool used to assess autonomic function, and provides insight into the contributions of the parasympathetic and sympathetic nervous system (PNS and SNS, respectively) to HR modulation (35). Coarse graining spectral analysis (CGSA) is a non-invasive frequency domain analysis method that yields both harmonic and non-harmonic components of the HRV signal. The harmonic portion of the spectrum is subdivided into very low frequency (VLF; harmonic noise), low frequency (LF; primarily represents sympathetic neural oscillations of HR), and high frequency (HF; vagal modulation of HR; 4) components, with total power (TP) reflecting the complete power of the harmonic spectrum (4). Although controversial, the ratio of LF: HF is said to provide insight into the sympathovagal influences contributing to the alterations in HR by the autonomic nervous system (35). The ratio of HF: TP is indicative of parasympathetic modulation of HR (22). CGSA allows for more accurate quantitative analysis of HRV by acquiring clearer peaks in the LF and HF components of the power spectrum (39). This type of analysis is particularly useful in clinical populations who have reduced harmonic spectral power and preserved non-harmonic or fractal power, such as those with HT (29).

The effects of aerobic training on heart rate variability (HRV) have been thoroughly investigated, and although the findings are somewhat inconclusive in young healthy individuals, the evidence suggests that older individuals and patient populations (i.e., post-myocardial infarction (post-MI) patients) experience marked improvements in HRV following aerobic, resistance and IHG training (9,13,18,33,34,35). For example, 8-weeks of cycling exercise and calisthenics (1 hour, 5 times per week at 80% HR_{max})

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significantly increased parasympathetic modulation of HR (increase HF power) and decreased sympathetic modulation of HR (decreased LF power) in 22 post-MI individuals (52 ± 7 years; 21). In 88 older (57 ± 6 years) post-menopausal women, 8- weeks of running and/or cycling (120 - 165 minutes, 3 - 4 times per week, at 50% VO$_2$max) significantly increased both sympathetic and parasympathetic modulation of HR (increased LF and HF power; 13).

The effects of resistance training on HRV have been investigated to a lesser degree; however, the results continue to support improvements in HRV with training in clinical populations. In an early study examining the effects of 3 months of resistance training (whole body circuit training, at a moderate intensity, 3 times per week) in 39 individuals with chronic heart failure (65 ± 11 years; 23), significant increases in parasympathetic tone and reductions in sympathetic tone were observed following training (increase in HF power and decrease in LF power). More recently, the effects of 16-weeks of resistance exercise (30 minutes circuit training, 8 - 12 repetitions, 50-80% of 1 repetition maximum, 2 times per week) were examined in 19 women (27 - 60 years old) with Fibromyalgia who had blunted pre-training HRV (9). Investigators observed increases in total autonomic modulation of HR (TP) and increased parasympathetic control of HR (HF power) post-training.

To date, only one study has investigated the effects of IHG training on HRV and like with the aerobic and resistance training literature, this form of training also appears to positively influence autonomic modulation of HR. For example, following 10-weeks of IHG training (4, 30% MVC contractions, sustained for 2-minutes with alternate hands, separated by a 1-minute rest period, 3x/week), investigators found an increase in resting vagal tone (increase in HF power) in 17 older (60 - 80 years old) hypertensives (some of whom were on medication to treat their hypertension; 35).

Over 29% of people in the United States have HT, yet only 78% of these individuals are aware of their HT. Importantly, of those who are aware of their HT, only 64% are successfully treated to target ABP values (≤ 135/85 mmHg and lower) (26). Importantly, reductions in SBP and DBP of 2 mmHg reduce the risk of stroke by 14% and 17%, respectively, and the risk of coronary artery disease by 9% and 6%, respectively. As hypertensive individuals have elevated ABPs and marked reductions in HRV, improvements in ABP and/or HRV following IHG training may have clinical relevance. With this knowledge, 3 important, novel research questions emerge: in a randomized controlled trial of *medicated* HTs 1) Does IHG training reduce resting ABP? 2) Does IHG training improve ambulatory ABP? and, 3) Does IHG training improve resting HRV? Therefore, the purpose of the current randomized controlled study was to address the hypotheses that IHG training lowers resting and ambulatory ABP and improves resting HRV in medicated hypertensives.

Methods:

Study Participants. Twenty-five individuals, aged ≥18 years, who had been receiving pharmacotherapy for HT for at least 4 months, were recruited to participate in this study. Baseline characteristics of participants are displayed in Table 3. Five individuals voluntarily withdrew from the study due to time restraints (2 in IHG training group, 3 in the control group). Individuals with diabetes, a paced heart rhythm at rest, frequent ventricular premature beats, heart failure, and those who had any physical limitation that would have prevented them from performing IHG exercise, were excluded from the study.

Table 3: Baseline characteristics of participants

Participants	All (N = 25)	Training Group (*n* = 11)	Control Group (*n* = 9)
Females (*n*)	13	4	6
Age (years)	61 ± 8.2	60.0 ± 8.5	62.7 ± 6.1
BMI (kg/m^2)	30.8 ± 7.2	31.7 ± 7.5	31.0 ± 8.8
Systolic Blood Pressure (SBP; mmHg)	114.6 ± 11.3	113.9 ± 12.7	117.8 ± 14.3
Diastolic Blood Pressure (DBP; mmHg)	67.5 ± 10.3	60.7 ± 11.6	67.5 ± 4.2
Heart Rate (beats/min)	66.9 ± 10.8	62.8 ± 8.5	69.5 ± 15.3
Medication: (*n*)			
Diuretic	2	2	1
Angiotensin Converting Enzyme (ACE)	3	1	1
Aldosterone Receptor Blocker (ARB)	3	1	1
Calcium Channel Blocker (CCB)	3	2	0
Diuretic + ACE	1	1	0
Diuretic + ARB	3	1	1
ACE + Beta Blocker (BB)	3	1	1
ARB + CCB	1	0	1
ARB + BB	1	1	0
Diuretic + ACE + BB	2	1	1
Diuretic + ARB + BB	1	0	1
Diuretic + ARB + CCB	1	0	0
Diuretic + ARB + CCB + BB	1	1	0

Values are mean ± S.D

Study design. The University of Windsor Research Ethics Board approved this randomized controlled investigation, and all participants provided written informed consent and completed a medical questionnaire. Upon review of the medical questionnaire and establishment of eligibility, participants underwent familiarization of all testing procedures. Participants were then randomized to an IHG training group or a non-exercising control group. In order to blindly randomize participants into groups, GraphPad software was employed (GraphPad Prism 5, GraphPad Software Inc, La Jolla,

CA, USA). Participants assigned to the IHG training group were instructed on proper IHG exercise techniques.

Following group assignment, all participants underwent baseline-testing procedures, which were repeated after 4- and 8- weeks of IHG training (or no training for the control group).

Exercise Training Protocol. Participants assigned to the IHG training group trained 3 times per week, for a total of 8 weeks. Two training sessions per week took place under the direct supervision of an exercise trainer, and the third session was conducted in the participants' home. Participants were provided with detailed instructions to ensure proper at home training, and were instructed to record their exercise, nutritional, and medication data in exercise log books to ensure consistency throughout the intervention period.

Each training session took approximately 30 minutes. Prior to the on-site training session, participants had their ABP measured (Dinamap ProCare 100, Critikon, Tampa, FL, USA); this data was not used for analysis. Participants then performed a bout of IHG exercise: 4 sets of 2-minute isometric contractions (using alternate hands) were performed on a programmed handgrip dynamometer (ZonaPLUS, Zona HEALTH, Boise, ID, USA) at 30% maximal voluntary contraction (MVC; determined at the onset of each exercise session via electronic linear load cells contained within each IHG device), each separated by a 1-minute rest interval (20,23).

Participants randomized to the non-exercising control group visited the laboratory 2 times per week to have their ABP measured to ensure equal face-time with investigators (25).

Testing Protocol. As previously mentioned, all participants underwent testing at baseline, and after 4- and 8- weeks of IHG training (or no training for the control group).

To minimize the influence of external factors on the cardiovascular measures, participants were asked to refrain from the consumption of alcohol and exercise for 24 hours prior to each testing session, and to avoid caffeine consumption for 12 hours prior (20). All testing was conducted in the morning, in a quiet, temperature-controlled room, following a light breakfast. On testing days, all participants were asked to void their bladder prior to the testing session to minimize the effects of bladder distension on blood pressure (8).

Resting ABP and HR were measured after 10 minutes of seated rest (Dinamap ProCare 100, Critikon, Tampa, FL, USA; 3). R-R interval HR data was then recorded for 10 minutes for later analysis of resting HRV, using standard electrocardiography (ECG), whereby a set of 3 electrodes was placed on the participants' chest (22). To minimize lead placement errors, the same investigator performed the ECG setup at all testing sessions (5). After measuring resting ABP, HR and HRV, the participants were fitted with an ambulatory ABP monitoring device on their right arm, which monitored ABP and HR for 24-hours (Spacelabs 90207 Ambulatory Blood Pressure Monitor, SpaceLabs Inc., Redmond, WA, USA).

Data Analysis:

Resting ABP and HR: Four ABP and HR values were acquired, each separated by 2 minutes (Dinamap ProCare 100, Critikon, Tampa, FL, USA) by the same trained investigator following a 10-minute rest period (3). The latter 3 measures were averaged and used in the final analysis.

Ambulatory ABP and HR: ABPs and HRs were recorded 2 times per hour during daytime hours (6am - 10pm), and 1 time per hour during nighttime hours (10pm - 6am) over a 24-hour period using an ambulatory brachial artery oscillometric device (Spacelabs 90207 Ambulatory Blood Pressure Monitor, SpaceLabs Inc., Redmond, WA,

USA) (19). Values were averaged over the entire 24-hour ambulatory period (mean 24-hr), and during each time period (daytime and nighttime).

Resting HRV analysis: Beat-to-beat HR was acquired using standard electrocardiography (ECG), as previously described (22). HR signal output was sampled at a frequency of 1,000 Hz. The analogue signals were converted to digital signals using a data acquisition board (PowerLab 8/30, ADInstruments Inc., Colorado Springs, CO, USA) for off-line beat-to-beat analysis. Ensemble averages of 256 beat sequences were taken from a minimum time series of 400 beats (22). Ectopic beats were edited and replaced via linear interpolation from adjacent cardiac cycles (22). Only tracings with ≤5% ectopy-corrected beats were accepted for analysis (22), thus 2 of the 20 participants were excluded from the HRV analysis (both of whom were in the training group). To assess HRV, these R-R (i.e. pulse) intervals were then submitted to CGSA (22,39).

Statistical Analysis:

One-way ANOVAs (group) of baseline resting ABP, 24-hour ambulatory ABP and HRV were employed to determine if baseline differences existed between the training and control groups. As no differences were revealed ($P ≥ 0.05$), two-way ANOVAs (group x time) were used to analyze resting ABP (SBP, DBP) and HR, 24-hour ambulatory ABP (24-hour mean ABP, nighttime ABP, and daytime ABP) and resting HRV (VLF, LF, HF, TP, LF: HF ratio, HF: TP ratio). Where applicable, post-hoc analyses were conducted using paired-sample t-tests, which used Bonferroni corrected alpha levels.

All data were re-assessed after separately controlling for, as between subject factors, gender (male or female), medication (single or multiple medications) and

baseline ABP (controlled to within the normal range (≤120/80 mmHg) or uncontrolled

(≥120/80 mmHg)).

The training group was further divided into IHG training responders, who experienced

clinically significant reductions in ABP (≥ 2 mmHg; 30), and non-responders (those who

did not achieve reductions in ABP ≥ 2 mmHg). One-way ANOVA (group) was employed

to determine if baseline differences existed between groups for baseline ABP, age, and

BMI. As no differences were observed ($P ≥ 0.05$), two-way ANOVAs (group x time) were

employed to analyze resting ABP (SBP, DBP) and HR. We did not re-categorize our

population into responders and non-responders for ambulatory ABP, as we were

unaware of any existing literature specifying clinically relevant reductions in ambulatory

ABP related to reduced CVD risk.

Statistical significance was set at $P ≤ 0.05$. Results are mean ± S.D., unless

otherwise specified. Analysis of data was completed using IBM (PASW) SPSS Statistics

18 (SPSS Inc., Chicago, IL, USA).

Results:

Effects of IHG training on resting ABP and HR

Following 4- and 8- weeks of IHG training (or no training for the control group), no

significant changes in resting SBP, DBP, or HR were observed in either the training

group or in the control group (all $P ≥ 0.05$). Results are shown in Table 4.

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Table 4: Resting SBP and DBP at baseline, after 4- and 8-weeks of training.

	Baseline	After 4-weeks of training	After 8-weeks of training
SBP (mmHg)			
Control Group	113.3 ± 11.8	111.4 ± 14.4	118.4 ± 15.5
Training Group	112.2 ± 11.0	110.9 ± 7.1	111.3 ±7.7
DBP (mmHg)			
Control Group	61.9 ± 12.4	60.6 ± 10.5	63.5 ± 12.4
Training Group	68.9 ± 7.0	66.9 ± 8.7	69.0 ± 7.4
HR (beats/min)			
Control Group	62.9 ± 8.6	59.9 ± 7.7	61.3 ± 9.0
Training Group	66.1 ± 12.0	65.6 ± 13.7	67.9 ± 14.7

Values are mean ± S.D; all $P > 0.05$. N = 20 (training group: n = 11; control group: n = 9).

When participants in the training group were divided into responders and non-responders, 6 of the 11 participants experienced clinically relevant reductions in SBP (~9.0 ± 5.2 mmHg), while 5 of the 11 showed clinically relevant DBP reductions (~2.0 ± 1.6 mmHg). Two-way analysis of variance of SBP revealed a significant interaction between time and group (P = 0.001). Post-hoc analyses showed a significant reduction in SBP (P = 0.008) from baseline to 8-weeks in the responder group, and no significant reductions in SBP (P = 0.07) in the non-responder group. No significant interactions or main effects were revealed for DBP or HR, for either group ($P > 0.05$) at any time point. The baseline characteristics of responders and non-responders, with respect to SBP, are shown in Table 5.

Table 5: IHG training responder versus non-responder baseline characteristics

N = 11	Responders (*n* = 6)	Non-responders (*n* = 5)
Females	3	1
Age (years)	59.0 ± 7.6	58.8 ± 9.5
BMI (kg/m^2)	35.7 ± 9.8	28.6 ± 2.9
Resting ABP (mmHg)		
SBP	115.2 ± 8.9	108.5 ± 12.7
DBP	67.6 ± 5.3	70.5 ± 8.9
HR (beats/min)	68.3 ± 8.4	63.4 ± 15.9
Medication: (*n*)		
Diuretic	1	1
ACE	0	1
ARB	1	0
CCB	1	1
Diuretic + ACE	1	0
ACE + BB	0	1
ARB + BB	1	0
Diuretic + ACE + BB	0	1
Diuretic + ARB + CCB + BB	1	0

Values are mean ± S.D.; all *P* > 0.05.

Effects of IHG training on 24-hour ambulatory ABP

Small reductions in 24-hour mean SBP, DBP and HR for the training group were noted, however, these findings were not statistically significant when compared to the non-exercising control group (all *P* > 0.05) at any time point. For 24-hour mean SBP, there was a trend towards a group and time interaction (*P* = 0.07) over the 8 week period. Nighttime SBP, DBP and HR did not significantly change from baseline (all *P* > 0.05) for either group with 4- or 8- weeks of IHG training, yet, again, there was a trend towards a group x time interaction for a reduction in nighttime SBP (*P* = 0.06) over the entire training period (8-weeks). For both groups, daytime SBP, DBP, and HR remained

unchanged after 4- and 8-weeks of IHG training (all P > 0.05). All ambulatory ABP results are shown in Table 6.

Table 6: 24-hour mean SBP and DBP at baseline, after 4- and 8-weeks of training.

Variables	Baseline	After 4-weeks of training	After 8- weeks of training
24-hour mean SBP (mmHg)			
Control Group	126.2 ± 10.4	130.4 ± 8.5	127.9 ± 9.5
Training Group	127.4 ± 10.1	125.6 ± 8.9	125.5 ± 8.6
24-hour mean DBP (mmHg)			
Control Group	71.4 ± 7.8	74.2 ± 8.4	71.7 ± 7.14
Training Group	76 ± 6.0	75.6 ± 6.0	74.4 ± 6.0
24-hour mean HR (beats/min)			
Control Group	62.8 ± 10.1	63.0 ± 8.5	62.2 ± 10.4
Training Group	68.3 ± 9.5	67.1 ± 9.7	67.6 ± 10.3
Daytime SBP (mmHg)			
Control Group	130.6 ± 11.5	134.0 ± 10.6	133.1 ± 10.9
Training Group	132.0 ± 8.8	130.5 ± 7.6	131.1 ± 8.9
Daytime DBP (mmHg)			
Control Group	75.1 ± 8.9	76.3 ± 9.5	75.2 ± 8.0
Training Group	80.0 ± 6.2	79.6 ± 6.8	79.5 ± 7.3
Daytime HR (beats/min)			
Control Group	66.2 ± 10.8	65.8 ± 9.3	64.4 ± 10.4
Training Group	71.3 ± 10.7	69.6 ± 11.1	71.0 ± 10.5
Nighttime SBP (mmHg)			
Control Group	117.9 ± 8.7	123.4 ± 7.7	119.0 ± 7.9
Training Group	120.0 ± 13.9	116.6 ± 12.5	116.0 ± 8.5
Nighttime DBP (mmHg)			
Control Group	65.1 ± 6.5	69.9 ± 6.9	64.7 ± 6.6
Training Group	69.2 ± 7.3	67.8 ± 6.1	65.6 ± 5.6
Nighttime HR (beats/min)			
Control Group	56.6 ± 9.3	57.4 ± 8.2	58.4 ± 10.5
Training Group	63.4 ± 9.6	62.5 ± 10.0	61.8 ± 9.6

Values are mean ± S.D.; all $P > 0.05$. N = 20 (training group: $n = 11$; control group: $n = 9$).

Effects of IHG training resting HRV

Following 4- and 8-weeks of IHG training, no significant differences were observed, in any indices of HRV (VLF, LF, HF, TP, LF: HF ratio and HF: TP ratio; all $P >$ 0.05). All data are presented in Table 7.

Table 7: Resting HRV indices at baseline, after 4- and 8- weeks of training.

	Baseline	After 4-weeks of training	After 8-weeks of training
VLF (ms^2)			
Training	203.7 ± 275.0	99.2 ± 86.0	113.0 ± 132.0
Control	158.0 ± 122.7	99.4 ± 86.2	98.6 ± 107.7
LF (ms^2)			
Training	86.9 ± 144.1	50.7 ± 33.6	47.7 ± 48.3
Control	108.2 ± 120.6	76.2 ± 64.3	47.7 ± 61.3
HF (ms^2)			
Training	65.0 ± 103.6	102.7 ± 119.6	83.8 ± 109.1
Control	93.0 ± 124.0	41.5 ± 33.2	73.1 ± 91.5
TP (ms^2)			
Training	355.6 ± 486.7	252.7 ± 211.8	244.4 ± 252.6
Control	359.2 ± 323.7	217.1 ± 124.1	219.4 ± 172.9
LF/HF (ms^2)			
Training	2.1 ± 2.1	0.8 ± 0.8	3.2 ± 5.6
Control	3.1 ± 6.1	3.8 ± 4.9	1.6 ± 2.5
HF/TP (ms^2)			
Training	0.3 ± 0.2	0.4 ± 0.2	0.4 ± 0.3
Control	0.2 ± 0.1	0.2 ± 0.2	0.3 ± 0.3

Values are mean ± S.D.; all $P >$ 0.05. N = 18 (training group: $n = 9$; control group $n = 9$).

Discussion:

Numerous small-scale studies in individuals with and without HT have investigated the effects of IHG training induced reductions in ABP, yet no randomized control trial to date has investigated its effects targeting solely medicated hypertensives. As 68% of individuals diagnosed with HT are receiving pharmacotherapy to treat their

HT, research focusing on this population is warranted. Secondly, no studies have investigated the effects of IHG training on ambulatory ABP, a clinically significant measure that provides a more comprehensive understanding of CVD risk (7). Furthermore, only one study has investigated the effects of IHG training on HRV, an important predictor of CVD related mortality (3,10,16,32), yet, many of the individuals in this study were not on medication for HT. Therefore, this study aimed to answer the novel questions: in medicated hypertensives 1) Does IHG training reduce resting ABP? 2) Does IHG training improve ambulatory ABP? and, 3) Does IHG training improve resting HRV?

Effects of IHG training on resting ABP and HR

Though the current study found small resting SBP reductions (~1 mmHg) for the training group, these findings did not reach statistical significance. The lack of SBP change was contrary to our hypothesis, and to the weight of published IHG studies in hypertensive individuals (25,35). Although reductions in resting DBP were not observed, these findings are in line with some of the current IHG literature. For example, Taylor and colleagues (35) reported significant reductions in resting SBP (~19 mmHg), but no significant reductions in DBP in older individuals with HT (mean resting ABP: ~156/82 mmHg; many of whom were unmedicated) following 10-weeks of IHG training (35). In accordance with findings from Taylor and colleagues, McGowan and colleagues, using a with-in subject study design, investigated the effects of IHG training on a group of medicated hypertensives (mean resting ABP: ~134/73 mmHg) and found reductions in SBP (~15 mmHg) and no significant reductions in DBP. Although numerous IHG studies in normotensive individuals cite post-training reductions in DBP (20,37), the discrepancy in DBP finding between the current study and the normotensive studies may likely be due to protocol differences, suggesting the IHG training stimulus over 8-weeks may not

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be sufficient to alter DBP in hypertensives. Alternatively, as a multilevel analysis performed to amalgamate previous IHG training studies performed in individuals with hypertension (25) showed a combined post-training DBP reduction of ~3 mmHg, it is possible that greater numbers of participants are required to detect a statistically significant reduction in DBP.

Why did we not replicate previously observed reductions in resting SBP in our population of medicated hypertensives? The lack of a reduction in SBP may be attributed to: 1) initial resting ABP, 2) IHG protocol, and/or 3) changes in physical activity and/or nutrition over the course of the study. As our study involved well-controlled medicated hypertensives (115/68 mmHg), the capacity for these individuals to respond to the IHG training stimulus may have been limited. Other studies that investigated the effects of IHG training in individuals with HT employed populations with higher initial ABPs, and as such, had a larger capacity for improvement (23,35). In support of this, a recent multilevel-analysis revealed that initial ABP had a significant effect on an individual's ABP response to IHG training, with individuals with higher ABPs showing larger reductions in resting ABP (25). Protocol differences may have also played a role in the lack of an observed reduction in SBP. Hypertensive individuals who are receiving pharmacotherapy may require a larger (greater % MVC) and/or longer (timed contraction, number of contractions and/or length of training) IHG stimulus. Finally, physical activity and/or nutritional changes may have contributed to the lack of SBP reductions in this study however, we consider this unlikely as both were monitored throughout the investigation.

As only 75% of individuals with HT experienced resting ABP reductions following exercise prescription (aerobic exercise training for 8 - 78 weeks, 2 - 6 times per week, at 50 - 80% VO$_2$max; 12), the training group was subdivided into individuals who responded

to IHG training (those that experience clinically significant IHG induced resting SBP reductions of ≥ 2 mmHg; 30) and those who did not respond (< 2 mmHg reduction in resting SBP). Although not statistically different, the responder group had higher baseline resting SBP (~6 mmHg) than those in the non-responding group. Again, this finding is in line with the weight of the evidence that suggests those with higher ABP experience the greatest hypotensive benefits from IHG training. There was also a marked difference, although not statistically significant, between the BMIs of the two groups. The responder group had a higher BMI (~36 kg/m^2) than did the non-responder group (~29 kg/m^2). BMI is associated with a persons' state of health, and as such, may have also played a role in their capacity to respond to an exercise intervention, as those in this study with higher BMIs experienced the greatest improvements in ABP following IHG training (24).

Ambulatory ABP

This is the first study to investigate the effects of IHG training on ambulatory ABP. In the current study, no statistically significant improvements were observed for any component of ambulatory ABP (mean 24-hr, daytime, or nighttime), a finding of which was in contrast to our hypothesis. Though not *statistically* significant (although a trend was noted), clinically relevant reductions in mean 24-hr SBP (~3 mmHg) (30) were observed following IHG training. Higher ambulatory ABPs increase one's risk of CVD (7), and as such, the reductions in mean 24-hour SBP in the current study may have the potential of reducing CVD risk (30). This reduction is in line with 24-hour mean ambulatory SBP reductions seen following aerobic exercise training (40 minutes of cycling, 3 times per week, for 10 weeks), though, like with IHG training, these reductions also did not achieve statistical significance (27).

For nighttime ambulatory SBP, the training group experienced post-training reductions that approached statistical significance, and thus the small size of the study

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may have contributed to this finding. Alternatively, ambulatory activities were not controlled during the testing days at baseline, and after 4- and 8- weeks of training (or no training for the control group), and may have minimized the potential to observe significant changes, however, we consider this unlikely, as participants reported no changes in daily physical activities throughout the course of the investigation.

Resting HRV

This investigation showed no significant improvement in any indices of HRV with IHG training. These finding are in contrast to our hypothesis that individuals would experience an improvement in HRV with IHG training, and contradict the findings of Taylor and colleagues (35), who noted marked improvements in vagal modulation of HR, in hypertensives, following 10-weeks of IHG training. An important distinction between the current study and the previously discussed study is that although both populations involved individuals with HT, in our study, <u>all</u> of our population was receiving pharmacotherapy for their HT. Autonomic function is known to improve with the prescription of ACE inhibitors and BBs (15,18), as these medications affect the autonomic nervous system. As participants in the study by Taylor and colleagues (35) were not all on HT medications, as a group they may have had a greater capacity to experience IHG training induced improvements in autonomic function. Furthermore, these individuals had hypertensive resting ABPs (> 150/80 mmHg), which suggests less effective control of resting ABP with pharmacotherapy, thus permitting a greater ABP and autonomic change with IHG training. As most of the individuals in this study were on an ACE inhibitor or BB, or a combination of an ACE inhibitor and a BB, they may have experienced maximum autonomic improvements from the pharmacotherapy and thus were unable to respond and/or had a blunted response to IHG training.

Conclusions and Future Directions:

These findings suggest individuals who are treated to within the normal ABP range (≤ 120/80 mmHg) may not experience ABP and HRV benefits from IHG training. Future studies should concentrate on populations of medicated and/or unmedicated hypertensives with ABPs above the normal range. Large scale trials aimed at these populations are necessary as they may reveal significant alterations in ABP, particularly ambulatory ABP, as our data suggests clinically relevant post-training improvements in ambulatory SBP (mean 24-hour and nighttime). This finding provides vital information regarding the limitations of assessing resting ABP alone, as the current study found no reductions in resting ABP. As ambulatory ABP is a better predictor of morbidity and mortality than resting ABP (7), it is important that future studies measure ambulatory ABP in addition to resting ABP.

Furthermore, the ability to classify individuals as responders or non-responders would provide effective and timely treatment regimes for HT individuals. Currently, only one study has investigated the predictability of IHG training success using cardiovascular reactivity tasks in normotensive individuals (26). Such studies should be conducted in hypertensives to establish whether this is an efficacious way of predicting IHG training hypotensive responses. Future studies should also aim to further stratify medication regimens to help provide a broader understanding of the effects of medication, alone or in combination, on the ABP and HRV responses to IHG exercise.

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CHAPTER 5: General Discussion

CVD is the leading cause of death in Canada, with HT significantly contributing to the risk of its development. HT is a complex pathophysiological disease, which rarely can be attributed to a known cause. Individuals with HT have elevated resting and ambulatory ABP experience PEH following many forms of exercise, and have reduced HRV.

The prevention and treatment of HT include lifestyle modifications and pharmacotherapy. Many individuals treated with pharmacotherapy are treated to within the normal ABP range, yet others remain unaffected (7). Lifestyle modifications, particularly exercise, have proven to be a successful means of lowering resting and ambulatory ABP (4,5,8) and improving HRV (1,2,3).

IHG training is a novel, less time consuming, simple exercise, shown, in individuals with and without HT, to markedly reduce resting ABP (6). The transfer of these effects to activities of daily living (i.e., ambulatory ABP), however, is currently unknown. Furthermore, individuals with HT have shown improvements in HRV with IHG training (8); however, the PEH and HRV responses post-IHG in HT individuals remain unknown, as are the effects of training on these responses.

The overall aim of this thesis was to answer the following research questions: 1) Does a bout of IHG elicit a PEH response and improvements in vagal modulation of HR in individuals medicated for HT, and do these responses change with 8-weeks of IHG training? and, 2) Does IHG training reduce resting ABP and 24-hour ambulatory ABP and improve vagal modulation of HR in medicated hypertensive?

Research Question 1: Does a bout of IHG elicit a PEH response and improve vagal modulation of HR in individuals medicated for HT, and do these responses change with 8-weeks of IHG training?

Our investigation found that a bout of IHG did not elicit a PEH response nor did it improve vagal modulation of HR. Following 4- and 8-weeks of training, the observed ABP and HRV responses were unchanged, and remarkably, they remained similar to the ABP and HRV responses observed at baseline, demonstrating a sustained response to IHG exercise.

Research Question 2: Does IHG training reduce resting and 24-hour ambulatory ABP and improve vagal modulation of HR in medicated hypertensive?

This investigation found no resting ABP or ambulatory ABP reductions following 4- or 8-weeks of IHG training, and all indices of HRV, including vagal HR modulation, were also unaltered with IHG training.

The population in this study was one of well-controlled medicated hypertensive individuals with ABPs within the normal range. These individuals may have experienced the maximum improvements in ABP and HRV with their HT medications, which may have limited their acute post-IHG responses, as well as their IHG training responses.

The IHG exercise stimulus may not have been great enough to elicit a PEH response or alterations in HRV following acute IHG exercise, or following IHG training in well-controlled medicated hypertensives. For this population, a greater stimulus (> 30% MVC), a longer duration of the sustained contractions (> 2-minutes) or their frequency (> 4 contractions), and/or a longer intervention period (> 8 weeks) may be needed to elicit the anticipated responses.

The results of this study should be interpreted with caution, as many individuals in the general population with HT are not controlled to within the ABP normal ranges. The participants in this study were among the 64% of those who are effectively controlled with medication for their HT, and as such, do not provide an accurate representation of the general hypertensive population.

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In summary, the primary findings of this investigation are: 1) IHG exercise does not elicit an acute PEH response nor does it alter post-IHG HRV in well-controlled medicated hypertensives, and these responses are unchanged with IHG training, and, 2) IHG training does not significantly reduce resting or ambulatory ABP, nor does it improve indices of HRV at rest in this population.

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Appendix A

University of Windsor

Individuals on Medication for HIGH BLOOD PRESSURE are invited to participate in a Research Study

---

Dr. McGowan and Cassandra Stiller-Moldovan at the University of Windsor are currently looking for individuals to participate in a study, approved by the Research Ethics Board, examining the effects of handgrip exercise on individuals medicated for high blood pressure.

We invite people who:
- Have high blood pressure
- Are on medication for high blood pressure

If you are interested and would like more information please contact:
Cassandra Stiller-Moldovan: (519)-253-3000 ext. 4979

519-253-3000 ext. 4979	519-253-3000 ext. 4979	519-253-3000 ext. 4979	519-253-3000 ext. 4979	519-253-3000 ext. 4979	519-253-3000 ext. 4979	519-253-3000 ext. 4979	519-253-3000 ext. 4979	519-253-3000 ext. 4979	519-253-3000 ext. 4979

Appendix B

Radio Advertisement:

Attention individuals with high blood pressure. If you are currently on medication for high blood pressure you may be eligible to participate in a research study at the University of Windsor conducted by Dr. McGowan and Cassandra Stiller-Moldovan. For more information please contact: Cassandra Stiller-Moldovan at 519-253-3000, ext 4979.

Appendix C

Researchers put squeeze on hypertension

DON LAJOIE
The Windsor Star

A team of University of Windsor researchers is inviting volunteers who are taking medication for hypertension to get a grip.

The team, led by associate professor Cheri McGowan and masters in human kinetics student Cassandra Stiller-Moldovan, is following up on resrach which suggests that regular flexing exercises using the wrist and hand can stabilize and lower blood pressure.

How and why this happens, and whether it may have applications for medical treatment, is the focus of the study. The team is looking for 30 volunteers who are on medication for hypertension to be tested.

NICK BRANCACCIO/The Windsor Star
Researchers Cassandra Stiller-Moldovan, left, and Cheri McGowan measure maximum voluntary contractions on human kinetics student Jeff Little in the physical activity and cardiovascular research lab Wednesday.

"We know that in young, healthy people the hand grip will lower blood pressure," said Stiller-Moldovan. "You do it three times a week for eight weeks, 12 minutes of simple, convenient exercise at a time. It can be done on your couch at home or you can take anywhere. It's promising but more research has to be done.... We don't know if it will be a substitute for medication."

Both scientists caution that the research to find out how and why these simple wrist-flexing exercises work is still in its infancy and that no one on medication should dump their pills and begin squeezing a rubber ball instead.

The task now, said McGowan, is to see if the results from testing healthy participants can be replicated with people who have hypertension.

"Further research could lead to new protocols for high blood pressure treatment," said Stiller-Moldovan, who received a $17,500 Banting and Best Scholarship prize from the Canadian Institute of Health Research for the project.

She said that it could provide a healthy and relatively inexpensive treatment for a serious health problem. Hypertension, a medical condition characterized by sustained levels of high blood pressure, affects one in five Canadians and can greatly increase the risk of cardiovascular disease, the leading cause of death in Canada. Yet, only 43 per cent of people with hypertension are aware they have the condition.

McGowan said the flexing effect was discovered as a result of "serendipity in science" when researchers in the U.S. were working with fighter pilots to find a way to raise their blood pressure to keep them from passing out during high-altitude flight. They found that, over time, the repetitive fist-pumping exercises they had devised seemed to have the opposite effect by reducing blood pressure.

Appendix D

University
of Windsor

thinking forward

Today's Date: April 3, 2009
Principal Investigator: Ms. Cassandra Stiller-Moldovan
Department/School: Kinesiology
REB Number: 09-060
Research Project Title: The effects of isometric handgrip exercise on post-exercise hypotension and heart rate variability in individuals medicated for hypertension
Clearance Date: April 2, 2009
Project End Date: April 1, 2010

Progress Report Due:
Final Report Due: April 1, 2010

This is to inform you that the University of Windsor Research Ethics Board (REB), which is organized and operated according to the *Tri-Council Policy Statement* and the University of Windsor *Guidelines for Research Involving Human Subjects*, has granted approval to your research project on the date noted above. This approval is valid only until the Project End Date.

A Progress Report or Final Report is due by the date noted above. The REB may ask for monitoring information at some time during the project's approval period.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the REB. Minor change(s) in ongoing studies will be considered when submitted on the Request to Revise form.

Investigators must also report promptly to the REB:
a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
b) all adverse and unexpected experiences or events that are both serious and unexpected;
c) new information that may adversely affect the safety of the subjects or the conduct of the study.

Forms for submissions, notifications, or changes are available on the REB website: www.uwindsor.ca/reb. If your data is going to be used for another project, it is necessary to submit another application to the REB.

We wish you every success in your research.

Pierre Boulos, Ph.D.
Chair, Research Ethics Board

cc: Dr. Cheri McGowan, Kinesiology
         Mark Curran, Research Ethics Coordinator

This is an official document. Please retain the original in your files.

Appendix E

LETTER OF INFORMATION FOR CONSENT TO PARTICIPATE IN RESEARCH

Title of Study: The effects of isometric handgrip exercise on post-exercise hypotension and heart rate variability in individuals medicated for hypertension.

You are asked to participate in a research study conducted by Ms. Cassandra Stiller-Moldovan and Dr. Cheri McGowan, from the Department of Kinesiology at the University of Windsor. Ms. Cassandra Stiller-Moldovan will be using this study to conduct research for her pursuit of a master's degree in Human Kinetics.

If you have any questions or concerns about the research, please feel to contact Dr. Cheri McGowan (faculty supervisor) at 519-253-3000 ext. 2451 or via email at mcgowanc@uwindsor.ca

PURPOSE OF THE STUDY

The main purpose of this study is to examine the blood pressure response immediately after a bout of isometric handgrip exercise in people who are taking medication to control their high blood pressure. We are also interested in seeing if this changes after 8 weeks of using the handgrip 3X per week. We also expect isometric handgrip training to lower your resting blood pressure, and to improve how your heart varies its rhythm.

PROCEDURES

If you volunteer to participate in this study, we would ask you to do the following things:

Eligibility/Consent/Familiarization Procedures

Visit 1:

After expressing interest in the study, if you meet the inclusion criteria, you will be invited to meet the investigators at the Applied Human Performance Laboratory (Department of Kinesiology, University of Windsor). At that time, you will be asked to read the consent form and information sheet on the study. After meeting with Ms. Cassandra Stiller-Moldovan and Dr. Cheri McGowan (study investigators), you will be familiarized with all portions of the investigation. If you are still interested in participating in the study, you will be asked to sign the consent form. Once you have given consent, you will fill out a brief medical questionnaire. At this time, we encourage you to ask any questions you have.

Visit 2:

To familiarize you with the procedures involved, you will undergo practice testing of resting blood pressure and heart rate acquisition. After this information has been collected, you will be randomized into one of two groups: 1) isometric handgrip training group, or 2) the control group (non-exercising). If you are randomized to the isometric handgrip training group, you will be shown how to properly perform a bout of isometric handgrip exercise. You will continue this exercise program for 8 weeks. If you are randomized to the control group, you will not exercise during the 8 week training period.

Measurement Procedures- 3rd visit to completion of investigation:

If you are randomized to the isometric handgrip group or the control group, you will undergo the same testing procedures. Testing will take place over 2 days before you start the study, in the Applied Human Performance Laboratory (Department of Kinesiology, University of Windsor). These procedures will be repeated in all participants after 4 week and 8 week of training. All measurements will take place in the

morning in a quiet, temperature-controlled room after a light, standardized breakfast (e.g., you will eat the same breakfast before each testing session), and you will take your medication at the same time. To minimize the influence of outside factors on these measures, you will be asked to avoid drinking alcohol and exercising for 24 hours before each testing session, as well as avoiding caffeine for 12-hours before the testing session. Your blood pressure medication will be monitored throughout the study, including your dosage, and the time of day you take the medication. Should your blood pressure medication change (dose, addition or removal of a medication) during the study, you must let one of the investigators know, and your results will be removed from the study. However, you may stay in the study until it is complete.

Day 1 (approximately 1 hour): After 10 minutes of seated rest, your resting blood pressure will be measured. We will take your blood pressure using a method that is similar to the way your doctor takes your blood pressure in their office. You will then participate in two tasks. The first will involve you placing your hand in cold water for 2 minutes. After this task, you will rest for 10 minutes in a seated position. Next, you will perform the second task, which involves mental arithmetic. You will be asked to subtract a 2-digit number from a number presented to you and say your answer aloud. You will be shown a total of 25 numbers, and will be given 5 seconds to complete each number. Following these tests, you will be sent home with a blood pressure device that will monitor your blood pressure for the next 24-hours. You will return the device the following morning.

Day 2 (approximately 3.5 hours): After 10 minutes of seated rest, your resting blood pressure will be measured, in the same way as it was on Day 1. Heart rate will be measured using standard electrocardiography, whereby a set of 3 electrodes will be placed on your chest. Heart rate will be recorded for 10 minutes. Following this data collection period, you will perform a bout of isometric handgrip exercise: you will perform 4 sets of 2-minute hand squeezing exercises (using alternate hands) on a programmed handgrip device at 30% of your maximum squeezing ability (which will be determined at the beginning of each exercise session with the handgrip device), separated by 1-minute rest intervals. During this exercise protocol, your heart rate will be recorded. Immediately following the last rest period, we will record your heart rate for 10 minutes. Following an additional 5-minute rest period, your blood pressure will be recorded. Your blood pressure will again be evaluated after 1 hour and 2 hours following the exercise session. Following the final blood pressure evaluation, we will send you home will a device that will record your blood pressure for the next 24 hours. The morning following the Day 2 testing session, you will return this device.

If you are randomized to the handgrip exercise group, you will train 3 times per week, for a total of 8 weeks. Two training sessions per week will take place under the supervision of an exercise trainer, where your resting blood pressure will be acquired, before each session, and the third session will be conducted in the your home. You will be provided with detailed instructions to ensure proper at home training, and will be instructed to record your exercise, nutritional, and medication data in exercise log books we will provide for you. If you are randomized to the control group, you will visit the laboratory 2 times per week for resting blood pressure measurements, for a total of 8 weeks.

Everyone will undergo identical testing procedures, which will occur on week 5, and week 9 of the study.

As mentioned above, you will be assigned to a handgrip exercise or a control group through random assignment. Testing visits will range between 30 minutes and 3.5 hours. For those randomized to the handgrip training group, training sessions will last no more than 30 minutes.

Visits to the University of Windsor for testing will take place during week 1, week 5, and week 9 of this study. You will be given a schedule of events for the study, to ensure your understanding and availability. You will be notified via email and/or phone call for follow-up sessions.

POTENTIAL RISKS AND DISCOMFORTS

If you are assigned to the handgrip training group, you may experience tendonitis in the trained tendons, however this risk is minimal if the exercise is properly performed. The blood pressure measurement procedure is non-invasive, as is electrocardiography for acquiring heart rate. However, in rare instances, you may experience numbness and/or tingling in the occluded limb while we are measuring your blood pressure and/or a minor rash from the heart electrode stickers we use to measure your heart rate.

POTENTIAL BENEFITS TO SUBJECTS AND/OR TO SOCIETY

You may or may NOT experience a lower resting blood pressure by participating in this study.

PAYMENT FOR PARTICIPATION

Subjects will not receive payment for participation in this study.

CONFIDENTIALITY

Any information that is obtained in connection with this study and that can be identified with you will remain confidential and will be disclosed only with your permission.

To ensure anonymity of subjects, following consent, all participants will be assigned an identification number. To ensure confidentiality, no mention of subject names will be used in any publication or presentation, and participants will be identified only by their identification number on all collection tools (electronic or otherwise). All paper data will be stored in a locked filing cabinet in the locked office of the principal investigators (HK 133, Department of Kinesiology, University of Windsor), and all electronic data will be stored in a locked laboratory (Applied Human Performance Laboratory, Department of Kinesiology, University of Windsor). Information stored on computer will be password-accessible only, and will be available only to the study investigators. With respect to final disposal, all paper records (including medical questionnaires) will be shredded.

PARTICIPATION AND WITHDRAWAL

You can choose whether to be in this study or not. If you volunteer to be in this study, you may withdraw at any time without consequences of any kind. You may also refuse to answer any questions you don't want to answer and still remain in the study. The investigator may withdraw you from this research if circumstances arise which warrant doing so.

FEEDBACK OF THE RESULTS OF THIS STUDY TO THE SUBJECTS

Subjects will have the option of receiving results from the study either by mail or email. Results will also be posted on the REB website in April 2010.

Web address: http://www.uwindsor.ca/reb
Date when results are available: April 2010

SUBSEQUENT USE OF DATA

This data may be used in subsequent studies. As data will be collected under the subject's identification number, data used for ongoing studies will ensure the privacy of the subjects.

RIGHTS OF RESEARCH SUBJECTS

You may withdraw your consent at any time and discontinue participation without penalty. If you have questions regarding your rights as a research subject, contact: Research Ethics Coordinator, University of Windsor, Windsor, Ontario N9B 3P4; Telephone: 519-253-3000, ext. 3948; e-mail: ethics@uwindsor.ca

SIGNATURE OF INVESTIGATOR

These are the terms under which I will conduct research.

_____   _____
Signature of Investigator   Date

Revised February 2008

Appendix F

CONSENT TO PARTICIPATE IN RESEARCH

Title of Study: The effects of isometric handgrip exercise on post-exercise hypotension and heart rate variability in individuals medicated for hypertension.

You are asked to participate in a research study conducted by Ms. Cassandra Stiller-Moldovan and Dr. Cheri McGowan, from the Department of Kinesiology at the University of Windsor. Ms. Cassandra Stiller-Moldovan will be using this study to conduct research for her pursuit of a master's degree in Human Kinetics.

If you have any questions or concerns about the research, please feel to contact Dr. Cheri McGowan (faculty supervisor) at 519-253-3000 ext. 2451 or via email at mcgowanc@uwindsor.ca

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The main purpose of this study is to examine the blood pressure response immediately after a bout of isometric handgrip exercise in people who are taking medication to control their high blood pressure. We are also interested in seeing if this changes after 8 weeks of using the handgrip 3X per week. We also expect isometric handgrip training to lower your resting blood pressure, and to improve how your heart varies its rhythm.

PROCEDURES

If you volunteer to participate in this study, we would ask you to do the following things:

Eligibility/Consent/Familiarization Procedures

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Visit 2:

To familiarize you with the procedures involved, you will undergo practice testing of resting blood pressure and heart rate acquisition. After this information has been collected, you will be randomized into one of two groups: 1) isometric handgrip training group, or 2) the control group (non-exercising). If you are randomized to the isometric handgrip training group, you will be shown how to properly perform a bout of isometric handgrip exercise. You will continue this exercise program for 8 weeks. If you are randomized to the control group, you will not exercise during the 8 week training period.

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Everyone will undergo identical testing procedures, which will occur on week 5, and week 9 of the study.

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POTENTIAL BENEFITS TO SUBJECTS AND/OR TO SOCIETY

You may or may NOT experience a lower resting blood pressure by participating in this study.

PAYMENT FOR PARTICIPATION

You will not receive payment for their participation in this study.

CONFIDENTIALITY

Any information that is obtained in connection with this study and that can be identified with you will remain confidential and will be disclosed only with your permission.

To ensure anonymity of subjects, following consent, all participants will be assigned an identification number. To ensure confidentiality, no mention of subject names will be used in any publication or presentation, and participants will be identified only by their identification number on all collection tools (electronic or otherwise). All paper data will be stored in a locked filing cabinet in the locked office of the principal investigators (HK 133, Department of Kinesiology, University of Windsor), and all electronic data will be stored in a locked laboratory (Applied Human Performance Laboratory, Department of Kinesiology, University of Windsor). Information stored on computer will be password-accessible only, and will be available only to the study investigators. With respect to final disposal, all paper records (including medical questionnaires) will be shredded.

PARTICIPATION AND WITHDRAWAL

You can choose whether to be in this study or not. If you volunteer to be in this study, you may withdraw at any time without consequences of any kind. You may also refuse to answer any questions you do not want to answer and still remain in the study. The investigator may withdraw you from this research if circumstances arise which warrant doing so.

FEEDBACK OF THE RESULTS OF THIS STUDY TO THE SUBJECTS

Subjects will have the option of receiving results from the study either by mail or email. Results will also be posted on the University of Windsor's Research Ethics Board (REB) website in April 2010.

Web address: http://www.uwindsor.ca/reb
Date when results are available: April 2010

SUBSEQUENT USE OF DATA

This data may be used in subsequent studies. As data will be collected under the subject's identification number, data used for ongoing studies will ensure the privacy of the subjects.

RIGHTS OF RESEARCH SUBJECTS

You may withdraw your consent at any time and discontinue participation without penalty. If you have questions regarding your rights as a research subject, contact: Research Ethics Coordinator, University of Windsor, Windsor, Ontario, N9B 3P4; Telephone: 519-253-3000, ext. 3948; e-mail: ethics@uwindsor.ca

SIGNATURE OF RESEARCH SUBJECT/LEGAL REPRESENTATIVE

I understand the information provided for the study **"**The effects of isometric handgrip exercise on post-exercise hypotension and heart rate variability in individuals medicated for hypertension" as described herein. My questions have been answered to my satisfaction, and I agree to participate in this study. I have been given a copy of this form.

_____
Name of Subject

_____   _____
Signature of Subject   Date

SIGNATURE OF INVESTIGATOR

These are the terms under which I will conduct research.

_____   _____

Signature of Investigator   Date
Revised February 2008

Appendix G

Medical Questionnaire

Last Name_____   First Name_____

Address_____ City _____ Province _____

Sex (please circle): M   F   Height:_____   Weight: _____

Date of Birth_____   Home Phone #   (_____) _____   Postal Code _____
       Month   Year

FOR EMERGENCY NOTIFY: Name_____   Relationship_____

Address_____   Phone_____

Family Doctor's Name_____   Date of Last Physical _____

                                                 Month   Year

Please Check Yes or No: Yes   No

1. Have you ever been hospitalized? --o   o
    If yes, please specify?

    _____

    Have you ever had surgery? --o   o
    If yes, please specify?

    _____

2. Are you presently taking any medications or pills (including aspirin)?--------------------------- o   o
    If yes, please specify?

    _____

    Are you presently taking any vitamins or supplements?-- o   o
3. Do you have any allergies (medicine, food, bees or other stinging insects)?------------------ o   o
    If yes, please specify?

    _____

4. Have you ever passed out during or after exercise?--- o   o
    Have you ever been dizzy during or after exercise?-- o   o
    Have you ever had chest pain during or after exercise?--- o   o
    Do you have high blood pressure?--- o   o
    If yes, are you being treated for this condition?

    _____
    Have you ever been told that you have a kidney problem? --- o   o
    Have you ever been told that you have joint instability? -- o   o
    Have you ever been told that you have a stomach problem? --------------------------------------- o   o
    Have you ever been told that you have a heart problem? --- o   o
    Have you ever been told that you have a heart murmer? -- o   o
    Do you have a machine that regulated your heart beat? -- o   o
    Have you ever had racing of your heart or skipped heartbeats? ---------------------------------- o   o
    Has anyone in your family died of heart problems or a sudden death before age 50? ------ o   o
5. Do you have any skin problems (itching, rashes, acne)? -- o   o
    If you get a cut, does it take you a long time to stop bleeding?----------------------------------- o   o
    If you experience a blow to a muscle, to you bruise easily? -------------------------------------- o   o
6. Do you have Diabetes? -- o   o
7. Do you have Asthma or any other breathing problems? --- o   o
    If yes, please specify?

    _____

8. Do you have any type of cardiovascular disease? --- o   o
      If yes, please specify?

      _____
9. Have you had any other medical problems (infectious mononucleosis, etc.)? ----------------o   o
10. Have you had any medical problems since your last physical? ----------------------------------o   o
11. Do you smoke? --o   o

Please explain any physical limitations that may prevent you from completing this study.

_____
_____
_____
_____

Appendix H

University
of Windsor

At HOME JOURNAL:

Subject ID:_____

Date	What was your maximum contraction value?	Did you complete two sets with each hand?	Time you took your medication	Have you had any medication changes? If yes, please describe.	Have you had any dietary changes? If yes, please describe.	Have you had any physical activity changes? If yes, please describe.

VITA AUCTORIS

Casssandra Stiller-Moldovan was born April 15, 1985 in Tecumseh, Ontario to Gabriele Stiller and William Moldovan. She graduated from Goddard High School (Roswell, New Mexico) in 2002. Following high school, she completed an honours degree in Biochemistry from the University of New Mexico, (Albuquerque, New Mexico) and graduated in 2006. Cassandra then returned to Windsor, where she is currently a candidate for the Master's degree in Human Kinetics at the University of Windsor and hopes to graduate in Fall 2010.