The effects of isometric handgrip training on carotid arterial compliance and resting blood pressure in postmenopausal women

Michael Gregory
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The effects of isometric handgrip training on carotid arterial compliance and resting blood pressure in postmenopausal women

By:
Michael Gregory

A Thesis
Submitted to the Faculty of Graduate Studies through the Faculty of Human Kinetics in Partial Fulfillment of the Requirements for the Degree of Master of Human Kinetics at the University of Windsor

Windsor, Ontario, Canada
2012
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The effects of isometric handgrip training on carotid arterial compliance and resting blood pressure in postmenopausal women

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September 10th, 2012
Author’s Declaration of Originality

I hereby certify that I am the sole author of this thesis and that no part of this thesis has been published or submitted for publication.

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Abstract

Reduced carotid arterial compliance (CAC) and elevated resting blood pressure (BP) above the normal (≥120/80 mmHg) increases postmenopausal women’s cardiovascular disease risk. Isometric handgrip training reduces resting BP across populations; however its influence on carotid arterial compliance (an independent CVD risk factor) remains unknown. This study sought to determine the effect of IHG training on CAC and resting BP in postmenopausal women. CAC and resting BP were measured in 8 postmenopausal women (65 ± 6 years; mean ± standard deviation) with elevated BP before and after 8-weeks of IHG training (n=5; baseline systolic BP 138 ± 12 mmHg) or sham-training (n=3; baseline systolic BP 142 ± 22 mmHg). CAC and resting BP remained unchanged following the intervention (P > 0.05), however, clinically significant reductions in resting systolic BP and diastolic BP and were observed. These findings highlight the use of IHG training as an adjunct therapy for this population, however, future study is warranted.
Acknowledgements

This thesis is dedicated to my family...

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<th>Description</th>
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<tbody>
<tr>
<td>ABP</td>
<td>Ambulatory blood pressure</td>
</tr>
<tr>
<td>ACEIs</td>
<td>Angiotensin converting enzyme inhibitors</td>
</tr>
<tr>
<td>ACCh</td>
<td>Acetylcholine</td>
</tr>
<tr>
<td>ADMA</td>
<td>Asymmetrical dimethylarginine</td>
</tr>
<tr>
<td>AIx</td>
<td>Augmentation index</td>
</tr>
<tr>
<td>ANG II</td>
<td>Angiotensin II</td>
</tr>
<tr>
<td>ANP</td>
<td>Atrial natriuretic peptide</td>
</tr>
<tr>
<td>ANS</td>
<td>Autonomic nervous system</td>
</tr>
<tr>
<td>ARB</td>
<td>Adrenergic receptor blocker</td>
</tr>
<tr>
<td>AT</td>
<td>Aerobic training</td>
</tr>
<tr>
<td>BB</td>
<td>Beta blockers</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>Ca$$^{2+}$$</td>
<td>Calcium ion</td>
</tr>
<tr>
<td>CAC</td>
<td>Carotid arterial compliance</td>
</tr>
<tr>
<td>CC</td>
<td>Central command center</td>
</tr>
<tr>
<td>CCB</td>
<td>Calcium channel blocker</td>
</tr>
<tr>
<td>CCC</td>
<td>Cardiovascular control centre</td>
</tr>
<tr>
<td>CO$_2$</td>
<td>Carbon dioxide</td>
</tr>
<tr>
<td>CSA</td>
<td>Cross-sectional area</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>CVS</td>
<td>Cardiovascular system</td>
</tr>
<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
</tr>
<tr>
<td>DC</td>
<td>Distensibility coefficient</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>ECM</td>
<td>Extra-cellular matrix</td>
</tr>
<tr>
<td>E</td>
<td>Epinephrine</td>
</tr>
<tr>
<td>$E_p$</td>
<td>Pressure-strain elastic modulus</td>
</tr>
<tr>
<td>ET$_1$</td>
<td>Endothelin-1</td>
</tr>
<tr>
<td>H$^+$</td>
<td>Hydrogen ion</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate</td>
</tr>
<tr>
<td>HRT</td>
<td>Hormone replacement therapy</td>
</tr>
<tr>
<td>HT</td>
<td>Hypertension</td>
</tr>
<tr>
<td>IHG</td>
<td>Isometric handgrip</td>
</tr>
<tr>
<td>MAP</td>
<td>Mean arterial pressure</td>
</tr>
<tr>
<td>mmHg</td>
<td>Millimeters of mercury</td>
</tr>
<tr>
<td>MMP</td>
<td>Matrix metalloproteinase</td>
</tr>
<tr>
<td>MVC</td>
<td>Maximal voluntary contraction</td>
</tr>
<tr>
<td>NE</td>
<td>Norepinephrine</td>
</tr>
<tr>
<td>NO</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>NT</td>
<td>Normotensive</td>
</tr>
<tr>
<td>PP</td>
<td>Pulse pressure</td>
</tr>
<tr>
<td>PNS</td>
<td>Parasympathetic nervous system</td>
</tr>
<tr>
<td>PWV</td>
<td>Pulse wave velocity</td>
</tr>
<tr>
<td>Q</td>
<td>Cardiac output</td>
</tr>
<tr>
<td>RAAS</td>
<td>Renin-angiotensin-aldosterone system</td>
</tr>
</tbody>
</table>
ROS
RT
SBP
SNS
STAI
STAI-S
STAI-T
SV
TGF-β
TPR
VSMC

Reactive oxygen species
Resistance training
Systolic blood pressure
Sympathetic nervous system
State-trait anxiety inventory
Emotional state inventory
Anxiety trait inventory
Stroke volume
Transforming growth factor beta
Total peripheral resistance
Vascular smooth muscle cell
Chapter 1: Introduction and Literature Review
1.1 Cardiovascular Disease

Cardiovascular disease (CVD) has been identified as the overall leading cause of death in the world \(^{(1)}\). In 2008, CVD-related mortality accounted for approximately 30% (17.7 million) of the total global deaths, with projections suggesting that by 2030 this number could reach upwards to 23.6 million deaths per annum \(^{(1)}\). CVD places a significant burden on the Canadian health care system as well \(^{(2)}\), where approximately 30% of the overall mortality for the nation in 2009 occurred as a result of CVD-related complications \(^{(3)}\).

It has recently been suggested that CVD is responsible for approximately 40% of the deaths of Canadian women \(^{(4)}\). The relative-risk of developing CVD in these women has been found to increase four-fold following the transition into menopause \(^{(4)}\), suggesting the importance of directing treatment around this age-determined milestone, where appropriately timed treatment(s) may be the most effective means in attempting to manage and/or prevent CVD in this population.

There are a myriad of identified risk factors, yet, approximately 80% of all CVD-related mortality is associated with arterial dysfunctions and/or disorders \(^{(5)}\). These pathologies can stem from unhealthy lifestyle choices, including excessive alcohol consumption, habitual tobacco smoking, sedentary lifestyle, unhealthy and/or high sodium diets, and excessive stress. Sustaining these poor lifestyles can lead to the development of hypertension (HT) \(^{(6)}\), which is considered by the Public Health Agency of Canada as one of the most important, primary risk factors associated with the development of CVD \(^{(6)}\).
1.1.1 Hypertension

HT is a chronic condition, characterized by elevated arterial blood pressure (BP) readings that are sustained for a prolonged duration \(^{(6)}\). Chronically sustained HT can result in damage to the vasculature and can produce a number of long-term complications that increase an individual’s risk for developing clinically significant CVD, which include stroke, heart failure, peripheral arterial disease, systolic, diastolic heart failure and chronic renal failure \(^{(7-9)}\). HT afflicts over 7.2 million Canadians \(^{(6)}\), the majority of whom are women. By the 6\(^{th}\) decade of life, the decade coinciding with menopause \(^{(10)}\), the prevalence of HT in women exceeds that of men \(^{(6)}\). Importantly, although HT is associated with increased rates of all-cause mortality among all Canadian adults \(\geq 20\) years of age, these rates are 34\% higher in females \(^{(6)}\).

HT affects all age groups, but the relative risk of establishing this CVD risk-factor tends to increase as one ages \(^{(6)}\). Age-specific prevalence rates are similar across the sexes for individuals younger than 50. For example, Vasan et al., \(^{(11)}\) alarmingly reported that 90\% of the middle-aged and older men and women participating in the Framingham Heart Study (a longitudinal cohort study), were likely to develop HT over the remaining years of their life. However, rates for women are increasingly higher than their male counterparts following the age of 55 and onwards \(^{(6)}\). Nevertheless, identifying individuals who are at an elevated risk of establishing sustained HT and implementing the appropriate measures to properly manage the progression of the disease early-on can reduce the risk of developing HT-related complications and CVD \(^{(6)}\). Furthermore, elevations in systolic blood pressure (SBP) by an increment of 20 mmHg or diastolic blood pressure (DBP) by an increment of 10 mmHg within the range of 115/75 mmHg to 120/80 mmHg can
185/115 mmHg doubles the risk of CVD for individuals between the ages of 40 and 70 years\(^9\). Therefore, implementing a HT-management plan that can facilitate modest decrements in resting BP in those who have been diagnosed with, or are at risk for the development of HT can reduce the risk of acquiring severe, cardiovascular-related complications, such as heart and renal failure, stroke and others\(^{6,12}\).

### 1.1.2 Arterial Blood Pressure

Arterial BP is described as the force that the blood exerts on the arterial walls during its transit through the cardiovascular system (CVS)\(^6\). Arterial BP is commonly described by two numbers, systolic and diastolic blood pressure. SBP is the pressure that the blood exerts on the arterial walls during the contraction phase of the cardiac cycle, coinciding with peak systole, whereas DBP is the pressure that the blood exerts on the arterial walls during the relaxation phase of the cardiac cycle, coinciding with diastole\(^6\).

#### Mean Arterial Pressure

Mean arterial pressure (MAP) describes the average BP within the CVS of an individual\(^{13}\). The MAP is slightly lower than the simple arithmetic average of SBP and DBP, due to the relative time spent during systole and diastole throughout the cardiac cycle. Systole (ventricular contraction) encompasses 1/3\(^{rd}\) of the cardiac cycle, while diastole (ventricular relaxation) spans the remaining 2/3\(^{rd}\)\(^{13}\). Because of this transitional relationship between systole and diastole through the cardiac cycle, MAP is thusly determined by the following equation: MAP = 1/3(SBP) + 2/3(DBP)\(^{13}\).

MAP is also represented as the product of the haemodynamic, mathematical relationship between cardiac output (Q) and total peripheral resistance (TPR), which is expressed by the following equation: MAP = Q x TPR \(^{13}\).
The interplay between modifications to either Q or TPR will produce changes to MAP, ultimately resulting in either an elevation or a reduction of arterial BP, where increases in Q, TPR or both will provide the appropriate stimulus to elevate BP (13).

**Cardiac Output**

Q represents the rate of arterial blood flow per minute that occurs as a result of cardiac contraction and the subsequent ejection of blood from the ventricles into the peripheral vasculature (13). Q is the product of heart rate (HR) and stroke volume (SV), and is expressed as millilitres of blood pumped per minute: Q = HR x SV (14). Q can also be derived through the rearrangement of the mathematical relationship between MAP and TPR, where: Q = MAP/TPR (14).

**Total Peripheral Resistance**

TPR describes the sum of the resistance exhibited by the vasoconstriction or vasodilation of the resistance arterioles of the peripheral vasculature throughout the systemic circulation (13). The tonic state of the vasculature is dependent upon the contractile state of the vascular smooth muscle cells (VSMC) that surround the arteries and veins. In order to initiate VSMC contraction, an action potential travels across the VSMC membrane which stimulates the opening of a voltage-gated calcium ion (Ca\(^{2+}\)) channel. This allows Ca\(^{2+}\) to flux into the cell, thereby increasing intracellular Ca\(^{2+}\) concentrations and stimulates the release of stored Ca\(^{2+}\) from the sarcoplasmic reticulum (14;15). The elevated levels of intracellular Ca\(^{2+}\) become sufficient to activate the Ca\(^{2+}\)-binding protein calmodulin, which subsequently binds to and activates myosin kinase. The activated myosin kinase phosphorylates myosin, thereby increasing the binding affinity of actin for myosin and stimulates VSMC contraction (14;15) (Figure 1: page 111).
TPR is estimated using the mathematical relationship between TPR, Q and MAP (TPR = MAP/Q). This relationship is a physiological representation of the physical laws governing flow, pressure and resistance that are used to describe laminar flow through a tube, Poiseuille’s Law: \( \Delta P = \frac{8 \mu LQ}{\pi r^4} \) \(^{(15)}\). A simple rearrangement of the formula suggests that any elevations in either TPR or Q would be sufficient to drive elevations in MAP.

TPR is influenced by a number of autonomic (sympathetic (SNS) and parasympathetic (PNS) nervous systems) and neurohumoral mechanisms [i.e., norepinepherine (NE), epinephrine (E), acetylcholine (ACh), and nitric oxide (NO), prostacyclin, adenosine, and endothelin-1 (ET1)], and will be elevated or reduced based on the interplay between these mechanisms and their relative influence on the vascular smooth muscle within the CVS.

1.1.2.1 Neural Control of Arterial Blood Pressure

Central Command and the Cardiovascular Control Centre

The neural influence on our CVS at the onset of, and during the participation in exercise is largely regulated by a central neural mechanism, known as the “central command center”, or CC \(^{(16)}\) (Figure 2; page 112). During periods of physiological stress, the CC innervates the cardiovascular control center (CCC; i.e. the medulla) via efferents to modify the activity of the autonomic nervous system (ANS) \(^{(14)}\). The ANS is separated into two functionally distinct branches, the SNS and the PNS. The SNS has a stimulatory effect on the CVS (increases HR, SV, and TPR), while the PNS has a quiescent effect on the body, ultimately acting to reduce HR, SV and TPR \(^{(14)}\). Both branches of the ANS work synchronously, where the elevation or reduction of one system
with respect to the other produces a physiological response. The SNS often acts in a “mass discharge” fashion, where all the portions of the SNS are activated simultaneously as a complete unit, while elevations of the PNS are usually the response to a specific localized stimulus (14).

Although CC and its association with changes in cardiovascular physiology commonly implies an effort-induced modulation of autonomic function, it has been noted that the cerebral cortical regions involved in the central cardiovascular command do not always require the parallel activation of central motor command systems to exert their influence. The magnitude of the CC-mediated CV-response during exercise can be independent of force production (eg. imagined exercise) and is mostly dictated by an individual’s perception of effort (17), a process that occurs even at the onset of exercise.

A ‘feed-forward’ mechanisms has been implicated in the preparation of the CVS at the onset or in an immediate response to exercise (14), however, it has been suggested that there would not be sufficient time for this feedback mechanism to be sent from the active peripheral muscles to innervate CV control within the brainstem (17). It has been postulated that an individual’s perception of the upcoming exercise bout could act as the feedback mechanism to establish the magnitude of the CC response to the exercise (17).

Primary regions within the cerebral cortex have been found to be associated with modulations in autonomic function in response to handgrip exercise and other stimuli, including the insular cortex and the anterior cingulate cortex (18) and the medial prefrontal cortex (18-20).

The insular cortex has efferent pathways into several well-recognized cardiovascular control regions (eg., the lateral hypothalamus, rostral ventrolateral medulla
and the nucleus of the solitary tract) and is able to modify both HR and BP upon activation \(^{(21)}\). The insular cortex and anterior cingulate cortex are both activated during static handgrip exercise by the CC independent of the muscle metaboreflex or elevations in BP \(^{(18)}\), suggesting that brief HG activates the right posterior insular region during but not immediately post-exercise, and that this activation covaries with changes in BP in response to the exercise \(^{(19)}\).

The thalamus is also intimately involved with the cardiovascular response to physiological stimuli, as the activation of the inferior regions of the thalamus (right and left inferior thalamic regions; analogous to ventroposterior regions that have been previously demonstrated to share connections with the insular cortex) have been found to occur in response to handgrip exercise in humans \(^{(19)}\). The thalamus monitors and controls cardiovascular responses, as changes in both BP and HR also influence thalamic activity (a large portion of the carotid baroreceptor-related neurons from the ventrocausal nucleus of the thalamus are involved with the integration of afferent baroreceptor information \(^{(22)}\), and the direct stimulation of these thalamic regions can result in increases in HR and BP in humans \(^{(23)}\).

The insular cortex and anterior cingulate cortex may work in concert as a CC network that functions to interpret an individual’s sense of effort and then facilitate the appropriate autonomic adjustments to prepare them for the upcoming physiological stress. The thalamic regions have a key role in the overall regulation of BP via baroreflex mechanisms and likely play a role in CC-induced changes in baroreflex function in response to exercise. To further this notion, recent work using a tendon vibration model to alter CC input \(^{(24)}\) found that the resetting of the carotid baroreceptor stimulus response
curve during exercise could be modified by selectively altering the CC activation. This work solidifies CC’s involvement in the carotid baroreceptor resetting during exercise (25;26) and suggests that exercises producing long-term modifications to CC outflow or input could result in an exercise-induced carotid baroreceptor sensitivity resetting and subsequently reduce BP (24). This phenomenon is important to note with respect to individuals with elevated resting BP performing isometric exercises, as previous work has demonstrated that increased BP is associated with alterations in baroreceptor reflex function (27;28) and that repeated performance of isometric exercise contributes to the resetting of the baroreceptors and reductions in BP (29).

The CCC monitors arterial BP and modifies the ANS in order to maintain optimal levels of blood perfusion to essential organs during activities of daily living. Not only does the CCC receive feed-forward information regarding the onset of stress from the CC, its response to a stimulus is also influenced via afferent signals sent from specific sensory receptors located within the periphery (14). These receptors are in place to monitor and respond to the physiological status of the peripheral circulation, and modify the ANS in response to locally produced stimuli. These receptors include the arterial baroreceptors, peripheral chemoreceptors and muscle afferent receptors (14).

**Arterial Baroreceptors**

Arterial BP is regulated and monitored in the CVS via the arterial baroreceptors (14). The arterial baroreceptors are located within the walls of the carotid artery, within the carotid sinus, and the wall of the aortic arch (14;30). These specialized receptors do not directly monitor arterial BP, but rather, are influenced when pressure differences in the arterial circulation result in conformational changes to the receptor. These
conformational changes occur as a result of reduced stretch of the receptor in response to modified arterial BP, and in turn, innervate the ANS via afferents sent to the CCC \(^{(14;30)}\).

The CCC is responsible for integrating the received information from the arterial baroreceptors with the originally initiated response to the current physiological demands, ultimately resulting in adjustments to the ANS to maintain cardiovascular homeostasis \((14;30)\).

**Peripheral Chemoreceptors**

Peripheral chemoreceptors are specialized sensory receptors that detect reductions in the oxygen saturation \(^{(31)}\), and modifications to carbon dioxide (CO\(_2\)) and/or hydrogen ion (H\(^+\)) concentrations \(^{(14)}\) of the arterial blood. These chemoreceptors are also located within the carotid and aortic bodies, monitoring the chemical composition of the blood as it leaves the heart and enters the peripheral circulation \((14;31)\). When a shift from homeostasis is detected, the chemoreceptors send modified signals via afferents to the CCC, which in turn, integrates this information and modifies the influence of the ANS (mainly the SNS) to increase vascular tone and arterial BP in an attempt to maintain adequate perfusion to essential organs while removing metabolic byproducts like CO\(_2\) and H\(^+\) \(^{(14)}\).

**Muscle Sensory Receptors**

Muscle sensory receptors have an important influence on BP regulation during periods of brief or prolonged exercise \(^{(32;33)}\). There are two main sensory receptors within the muscles: i) mechanoreceptors, which detect the mechanical compression or stretching based on the movements of the tissues adjacent to the receptor and ii) metaboreceptors, which detect the metabolic changes within the tissue that occur in response to a specific
action or stimuli \(^{(33;34)}\). These sensory receptors work in concert, monitoring and influencing the local environment of the working muscle by sending afferent signals concerning the relative work of the tissue to the CCC to modulate the ANS control of arterial BP \(^{(34)}\) in response to the demands of the activity.

The neural regulation of arterial BP involves the integration of a plethora of information formed within specific regions of the brain and that sent from peripheral sensory receptor afferents, all of which influence the CCC to initiate modifications in the control of arterial BP when attempting to maintain homeostasis within the CVS during periods of physiological stress.

### 1.1.2.2 Local Control of Arterial Blood Pressure

The local control of arterial BP involves the release and/or production of vasoactive compounds from sites within the CVS, their subsequent influence on the tonic state of the vascular smooth muscle that surrounds the resistance arterioles, and the resultant alterations in blood flow that occurs in response to the metabolic requirements of a specific tissue or muscle \(^{(35)}\). These vasoactive compounds therefore have the ability to directly modify arterial BP \(^{(14)}\). The most prominent locally produced substances that initiate vasodilation include potassium \(^{(35)}\), NO \(^{(14;36)}\), adenosine and the adenine nucleotides \(^{(14;35;37)}\), while ET\(_1\) \(^{(38)}\), prostacyclin and in special circumstances adenosine as well (via the A\(_3\) receptor within the peripheral vasculature and inflammatory respiratory disorders \(^{(39;40)}\)) are potent vasoconstrictors.

### 1.1.2.3 Hormonal Control of Blood Pressure

A large number of hormones are intimately involved with the regulation of arterial
BP, including catecholamines (released from the PNS, SNS and adrenal medulla), renin (released from the juxtaglomerular cells of the kidneys), aldosterone (released from the adrenal cortex), vasopressin (released by the pituitary gland), and atrial natriuretic peptide (ANP; released by the heart)\(^{(14)}\). All of these hormones work in concert with the local and neural control mechanisms to maintain arterial BP homeostasis.

**Norepinephrine**

The SNS neurons that act upon peripheral vascular beds release the catecholamine neurotransmitter NE, which activates the \(\alpha_1\)-adrenergic receptors within the vascular smooth muscle to initiate vasoconstriction\(^{(41)}\) (**Figure 3; page 113**). During this process, excess NE is released from the synapse in order to ensure a contraction within the target tissue. In order to ensure regulated functioning, \(\alpha_2\)-adrenergic receptors are located within the nerve terminal on the pre-synaptic neuron that monitor synaptic concentrations of NE and, when activated, have the ability to inhibit any further NE release\(^{(14;42)}\).

**Epinephrine**

E is recognized by both the \(\alpha\) and \(\beta\)-adrenergic receptors\(^{(14;42)}\). At the level of the heart, E acts upon the \(\beta\)-adrenergic receptors to enhance the sympathetic influence on cardiac function, increasing the contractile force and the speed of each cardiac contraction, thusly increasing HR and thereby increasing arterial BP\(^{(14;36;42)}\).

E also affects the vasculature in one of two ways; the activation of the \(\alpha\)-adrenergic receptors result in vasoconstriction in a similar manner as NE (increasing TPR and arterial BP), while E’s interaction with the vascular \(\beta\)-adrenergic receptors induces vasodilation by modifying intracellular \(\text{Ca}^{2+}\) concentrations\(^{(14;36;43)}\) (**Figure 4; page 114**).
**Acetylcholine**

ACh is released as the neurotransmitter of the PNS and is able to influence peripheral vascular tone by stimulating vasodilation within the vasculature of the sacral and cranial regions of the body through the activation of the muscarinic type III receptors (14;36;44) (Figure 5; page 115), however, this process contributes minimally to reductions in BP (45).

Within the heart, ACh is involved with the regulation of cardiac contractility and heart rate. The interaction of ACh with the muscarinic receptors of the myocardium results in a reduction in cardiac contractility and diastolic filling (14;36), while HR can be directly reduced via vagal innervation at the sinoatrial and atrioventricular nodes (14;36;44). These spontaneously depolarizing groups of cells control the rate that an action potential spreads through the myocardium to initiate each cardiac contraction, however, vagal innervation hyperpolarizes these regions and effectively slows the rate of depolarization within the tissue, slowing HR, reducing Q and decreasing arterial BP (14;36;44).

**The Renin-Angiotensin-Aldosterone System**

The kidneys have been widely recognized as an essential organ involved with arterial BP regulation by controlling total blood volume through urinary excretion and acting as an endocrine organ to produce hormones that modulate vascular tone. The primary endocrine functions of the kidneys are mediated through the renin-angiotensin-aldosterone system (RAAS) (14;36) (Figure 6; page 116). The majority of the RAAS involvement in BP regulation is accomplished through the activation of the potent vasoconstrictor angiotensin II (ANG II) in response to various stimuli including reduced BP, blood volume, elevated dietary sodium consumption, SNS innervation (14;36) and its
interaction with its receptors within the vascular smooth muscle (Figure 7; page 117).

Angiotensin II also acts at the level of the kidneys to elevate fluid and sodium retention in attempts to elevate blood volume and BP (14;36). ANG II furthers its function by stimulating the release of aldosterone from the adrenal cortex, which acts at the kidney to promote sodium retention in order to increase blood volume and arterial BP (14;46).

Lastly, ANG II is an important regulatory hormone for thirst (47), where arterial baroreceptor-mediated elevation in fluid intake results in an increase in total blood volume, which subsequently elevates arterial BP (47). When BP maintained, ANG II production is attenuated and the potentiation of thirst is inhibited, thereby reducing the endocrine-driven fluid intake and any further increases in total fluid volume (14;47).

**Vasopressin**

Vasopressin (a.k.a. anti-diuretic hormone or ADH) is a peptide hormone that is produced within the hypothalamus and secreted from the posterior pituitary in response to reductions in arterial BP (14). Vasopressin has two specific roles in BP regulation, i) acting as a vasoconstrictor to elevated BP upon activation of the vasopressin type I receptor within the vascular smooth muscle (Figure 8; page 118), and ii) promoting fluid retention via vasopressin type II receptor-mediated insertion of aquaporin 2 within the distal convoluted tubules and collecting ducts of the kidneys (14;46).

**Atrial Natriuretic Peptide**

When met with increased BP, the atria respond through the release of a locally produced peptide hormone, ANP. ANP acts to reduce BP in several ways, either by i) initiating vasodilation within the peripheral vasculature (54), ii) reducing aldosterone excretion from the adrenal cortex (14;48), iii) acting as an aldosterone antagonist to
stimulate sodium excretion at the level of the kidneys \(^{(14)}\), or iv) quieting SNS vascular innervation \(^{(14,48,49)}\) (Figure 9; page 119).

### 1.1.2.4 Genetic Basis for Arterial Blood Pressure Regulation

A large number of receptors and proteins are involved with the regulation of arterial BP. As such, several genetic polymorphisms involving these proteins have been identified to be associated with elevated resting BP – including those located on chromosome 17q12-21, the 122 cM region of chromosome 15 \(^{(50)}\), and the 70 cM region of chromosome 7 \(^{(51)}\). Although these regions are suspected to house BP regulatory genes, the specific gene candidates located within them remain to be identified \(^{(51)}\).

### 1.1.2.5 Effects of Anxiety on Arterial Blood Pressure

Elevations in BP have been found to occur in situations of excessive stress and/or anxiety as a consequence of elevated SNS activity induced by the emotional state \(^{(52)}\). An individual’s habitual level of anxiety has been found as a definitive link between environmental stress and the cardiovascular responses that may mediate the establishment of, and contribute to sustained elevations in BP \(^{(53)}\). Other emotional states (i.e. happiness or anger) also possess the potential to significantly elevate BP measurements in both healthy \(^{(54)}\) and clinical populations \(^{(55)}\), where the intensity of happiness has been found to be inversely related to SBP, while the degree of anxiety was positively correlated with DBP \(^{(56)}\). Furthermore, anxiety and depression are associated with established HT, where the physiological effects of these mental states contribute to the relative degree of BP elevation in these individuals \(^{(57)}\). The emotionally-mediated elevation in BP occurs as a result of SNS activation during periods of perceived un-comfort or distress, resulting in a catecholamine-mediated elevation in vascular tone and HR and contributes to elevated
arterial BP, HT, and CVD in these individuals (58).

In order to account for the potential impact that variations in the acute and chronic stress levels may have on cardiovascular measurements, questionnaires such as the State-Trait Anxiety Inventory (STAI) have been developed. This questionnaire allows for a tangible, daily and self-reported anxiety score that can represent the potential impact of emotional stress on BP regulation (59). The STAI consists of two, 20-item scales, which are used for measuring the intensity of anxiety as an emotional state (STAI-S) and the individual differences in anxiety proneness as a personality trait (STAI-T) (56). Anxiety levels assessed by the STAI have been identified as a psychological factor that holds an independent predictive value for changes in BP and HR as a result of the emotional status of pre-HT (60) and HT individuals (61).

1.1.3 Methods for Measuring Arterial Blood Pressure

The determination of resting BP has been historically used to stratify an individuals’ relative risk for HT-related CVD. Values for resting BP can be obtained through a variety of techniques, both invasive and non-invasive. More recently, ambulatory techniques have been developed to allow arterial BP monitoring over a consecutive 24-hour period in an attempt to account for an individual’s diurnal BP variations, and use this variability to construct a more accurate MAP measurement for individuals with suspected HT.

1.1.3.1 Invasive Blood Pressure Measurement

Invasive BP measurements involve the direct measurement of arterial pressure via the insertion of an intravascular cannula (hollow needle) into a peripheral artery, most commonly the radial, femoral or brachial artery (62). The cannula is connected to a
pressure-transducer, allowing the observer to monitor the patients BP on a beat-by-beat basis \(^{(62)}\). The invasive nature of this technique provides a myriad of risks, including thrombosis, increased risk of infection and bleeding at the insertion site \(^{(62)}\). The possibility of experiencing an adverse event during invasive BP measurements has resulted in the reservation of this technique solely for intensive-care situations primarily housed in clinical settings \(^{(62)}\).

### 1.1.3.2 Non-Invasive Blood Pressure Measurement

Non-invasive BP measurement techniques include i) stethoscope auscultation with sphygmomanometry, ii) automated oscillometry, iii) 24-hour ambulatory BP (ABP), iv) ultrasonography, v) the Peñá/Wesseling-method (Finapres/Portapres), and vi) arterial tonometry.

#### Sphygmomanometry and Auscultation

Sphygmomanometric auscultation has been considered the “gold-standard” non-invasive method for the determination of arterial BP. When sphygmomanometry is performed, an appropriate sized cuff is selected for each patient and is fitted snugly around the upper arm, oriented around the brachial artery at the elbow \(^{(63)}\). The cuff is manually inflated until the artery is completely occluded \(^{(63,64)}\). During auscultation of the brachial artery with a stethoscope, the examiner manually releases pressure from the cuff. When the pressure drops to a value below systolic arterial pressure, the 1\(^{st}\) Korotkoff sound is heard as the blood begins to once again flow through the previously occluded artery. The cuff pressure that allows for the 1\(^{st}\) Korotkoff sound to be heard by the examiner is representative of SBP \(^{(63,64)}\), while the pressure that allows for the 5\(^{th}\) Korotkoff sounds to be heard represents DBP \(^{(63,64)}\).
Although this technique continues to provide the most accurate measures of arterial BP, several limitations do exist. Firstly, the auditory assessment of Korotkoff sounds tend to give values for SBP that are lower and DBP that are higher than the true intra-arterial pressure, where some differences have been found to be as large as 25 millimetres of mercury (mmHg) between the two methods\textsuperscript{(63)}. Secondly, this technique is not appropriate in situations where the disappearance of sounds cannot reliably be determined, whether it is difficult to discern between each Korotkoff phase, or when sounds are still audible following the complete deflation of the cuff\textsuperscript{(63)}. Finally, when measuring resting BP using this technique with older patients who display wide pulse pressure (PP; the difference between SBP and DBP, where \( PP = SBP - DBP \)), the auscultatory gap phenomenon must be considered. This occurs when the Korotkoff sounds become imperceptible between systolic and diastolic pressure, but reappear as cuff deflation is continued\textsuperscript{(63;64)}. The auscultatory gap phenomenon can be eliminated by elevating the arm overhead for 30 seconds before inflating the cuff, then returning the arm back to the standard position to continue the measurement\textsuperscript{(63)}. This simple technique reduces the vascular volume in the measured limb and promotes greater inflow to enhance the Korotkoff sounds\textsuperscript{(63)}.

**Automated Oscillometry**

Automated oscillometry is based upon the observation of the oscillations in blood flow that are produced during the cardiac cycle\textsuperscript{(64)}. The process involves the use of a sphygmomanometric cuff that is programmed to automatically inflate and deflate while the oscillations in pressures are monitored via an electronic pressure sensor\textsuperscript{(64)}. The cuff is initially inflated to a pressure that exceeds systolic arterial pressure, and is gradually...
reduced over a 30 second period to a pressure that falls below diastolic pressure. The electronic pressure sensor automatically interprets the raw data and reports SBP and DBP following an algorithm-based computation (64).

The main advantage of this technique is that no transducer needs to be placed over the measured artery, therefore, accurate cuff orientation is not critical (63;64). Furthermore, this method is less susceptible to external noise (but not to low-frequency mechanical vibrations), can be used for ABP measurements, and eliminates any potential inconsistencies with respect to the hearing ability or the level of skill of the possessed by the examiner (63;64). However, the glaring limitation of this technique is that the amplitude of the oscillations depends on several factors other than BP, most specifically the arterial stiffness (63). Therefore, certain populations (i.e. the elderly) who display elevated arterial stiffness and wide PP may have their true MAP significantly underestimated (63).

Secondly, the algorithms used by the monitors to detect SBP and DBP are different between models and are not divulged by their manufacturers, a problem that is most concerning when comparing measurements taken using different devices that commonly produce significant differences between readings (63). Finally, the bladders deflate at a manufacturer-determined “bleed-rate”, which assumes a regular pulse between bleed steps as part of the algorithms used to determine BP (63), and hence, any subtle changes in cardiac performance during the measurement could skew the reported values. Although automated oscillometry has been traditionally used to measure resting BP, recent modifications have also allowed for this technique to be employed while individuals are mobile, reflecting their 24-hour ABP.
24-Hour Ambulatory Blood Pressure

ABP monitoring is a fully automated technique where arterial BP is recorded over an extended period of time (typically 24-hours) while individuals perform activities of daily living \(^{(63;64)}\). This technique has been used for decades in the research setting and has recently gained popularity as an important prognostic index for CVD-related morbidity and mortality \(^{(65;66)}\), where ABP assessments have been found to be more accurate in identifying those at elevated CVD-risk when compared to traditional resting BP measures \(^{(67)}\). ABP monitoring can provide information about three clinically significant measures of arterial BP, i) the overall daily average, ii) the diurnal variation, and iii) the short-term variability \(^{(64)}\). The standard equipment used for ABP monitoring includes a small automated oscillometric device coupled with an appropriate sized cuff, which is then attached to a belt and fixed to the participants arm around the brachial artery, respectively \(^{(63)}\). During a standard ABP monitoring session, arterial BP is measured from the non-dominant arm every 15 or 30 minutes over a 24-hour period, preferably on a work day \(^{(63)}\). After the 24-hour period, the total number of readings (reaching between 40 and 100) are downloaded into device-specific computer software, where the raw data is synthesized into a report that provides mean values for MAP, SBP, DBP, PP, and HR by hour and period: daytime (awake), nighttime (asleep), and a 24-hour overall summary \(^{(63)}\).

Despite the convenience of ABP monitoring, several limitations do exist. The device should be calibrated through a series of comparisons with arterial BP determined via mercury sphygmomanometry to ensure that the device is giving accurate readings (within 5 mmHg from the mercury readings) \(^{(63)}\). Furthermore, it is important to instruct the patient to hold their arm still at their side while the device is taking readings in order
to obtain the most accurate BP measures \(^{(63)}\). Finally, in order to account to individual variations in circadian rhythm, it might be helpful to ask patients to record a diary of activities, particularly with respect to when going to bed and when awaking in the morning \(^{(63)}\).

**Ultrasonography**

The use of ultrasonography for BP determination incorporates the use of an ultrasound transmitter placed directly over the brachial artery, underneath a sphygmomanometric cuff \(^{(64)}\). The cuff is inflated until blood flow through the brachial artery is occluded. Upon deflation, the movement of the arterial wall at peak SBP causes a Doppler phase shift in the reflected ultrasound, and DBP is recorded upon the cessation of arterial retraction \(^{(63;64)}\). This technique can also be used to detect the onset of blood flow at SBP, a method that has been proven to be of clinical significance in certain populations or individuals who prove difficult when using other BP measuring techniques (eg. patients with very faint Korotkoff sounds) \(^{(64)}\).

**Peñáz/Wesseling-method (Finapres/Portapres)**

The Peñáz/Wesseling-method is known as the Finapres/Portapres protocol. Developed in the 1970’s, this method exploits the principle of the “dynamic, unloaded arterial wall” \(^{(62;64;68)}\). The sizes of the arteries of the pointer finger are gauged via an infrared transmission plethysmograph mounted inside an inflatable cuff. The device is programmed to detect increases in the arterial diameters of the fingers with increasing BP; where appropriate increases in the air pressure within the cuff occur in order to maintain constant arterial diameters, keeping the arteries in a partially-opened state \(^{(62;64;68)}\). The oscillations in the cuffs’ pressure are measured with an electronic pressure...
gauge, which provides an indirect measurement of the intra-arterial pressure waveform and (together with the implementation of a pattern recognition program) the beat-by-beat SBP, DBP and MAP (62;64;68). Although somewhat cumbersome, the Finapres also enables readings to be taken over 24-hours while subjects are ambulatory, and thereby also provides insight into daily BP variability (63).

Although this method gives an appropriate estimate of the acute changes in BP, readings may be underestimated (or overestimated) in some populations when comparing the observed values to those taken from the brachial artery (63). Due to the cost, inconvenience, and relative inaccuracy for measuring absolute arterial BP, this method is considered inappropriate for use in clinical settings (63).

**Applanation Tonometry**

Applanation tonometry is another method for the non-invasive determination of arterial BP. This technique continuously monitors the fluctuations in arterial BP throughout the cardiac cycle through the detection and collection of the arterial PP waveform (69). The general principle of applanation tonometry is dependent upon the structural characteristics and anatomical location of the selected artery, it must be compressible (70) and must be located against a bone or rigid structure (63). For this procedure, a small applanation tonometer probe (Millar Instruments Inc., Houston, Texas, USA) is used as a pressure sensor and placed over either the radial (71) or the carotid (70;72-75) artery, where the tonometer must minutely compress or splint the artery against a bone in order to obtain an accurate PP waveform (63). This technique depends upon the Imbert-Fick law, which states that the internal pressure of a completely elastic spherical body equals the force exerted to flatten the body, divided by the flattened surface area (76). The
assumptions of this law enable applanation tonometry to estimate arterial BP with reasonable accuracy\(^{(76,77)}\) and can provide pressure waves that are almost identical to those obtained through intra-arterial measures\(^{(78)}\).

Although this technique has consistently shown to provide accurate insight on arterial BP, several limitations exist. Most importantly, the law by which this technique is based assumes that the artery in question is infinitely thin, perfectly elastic and perfectly flexible - none of which are true. Several other additional limitations also exist, including i) investigator expertise (e.g., the positioning of the tonometer probe must be precise and/or excessive hold-down force can skew arterial pressure readings), ii) motion artifacts may influence the forces translated from the artery to the tonometer, and iii) the calibration of the device requires the use of an external measurement device, such as an automated oscillometer\(^{(77)}\).

### 1.1.4 Pathophysiology of Hypertension

HT is considered the “silent-killer”, as it is currently labeled as the leading modifiable risk factor for CVD-related morbidity and mortality worldwide\(^{(6)}\). As previously discussed in Section 1.1.1 Hypertension, HT afflicts over 7.2 million Canadians\(^{(6)}\), where the majority of those affected are women who are in their 6\(^{th}\) decade of life - a decade that coincides with the onset of menopause\(^{(10)}\). Those with lower BP are also at risk, where a positive relationship between resting BPs as low as 115/75 mmHg and CVD risk has been identified for individuals between the ages of 40 and 70 years, which doubles for each 20/10 mmHg increase\(^{(8)}\). This risk is most applicable to women within this age group who have sustained higher than normal BP (NT; \(\geq120/80\) mmHg)\(^{(79)}\). Therefore, identifying individuals who are at an elevated risk for developing
HT (pre-HT postmenopausal women) are of utmost importance when trying to mitigate the burden that HT places on the Canadian health care system. As such, several hypertensive states have been identified and are defined below.

HT has no definitive symptoms; an individual is classified as HT following the accurate determination of elevated BP on two or more separate occasions, if an individual is on prescribed HT medications, or if they have been told, on 2 or more separate occasions, that they are HT by their health care practitioner \(^{(6)}\). The definition of HT has recently been re-evaluated; stratifying individuals into one of four BP groupings based on their resting BP measures, with healthy BP falling between \(\leq 120/\leq 80\) mmHg \(^{(9,80)}\). Individuals are classified as pre-hypertensive when displaying BP of 120-139/80-89 mmHg \(^{(9,80)}\). Although those found to be pre-hypertensive are not considered to have an established diseased state, this classification provides health care practitioners with an opportunity to intervene in individuals who are at an elevated risk for the development of HT \(^{(80)}\). As the condition progresses, individuals are considered to have Stage I HT when displaying BP between 140-159/90-99 mmHg, and considered Stage II HT (the most severe) when displaying BPs \(\geq 160/\geq 100\) mmHg \(^{(9,80)}\).

There is a widely held misconception that HT is a single disease and that it can be managed with a single choice of treatment. However, HT is a heterogeneous disorder that allows patients to be pathologically stratified according to their co-morbidities, and allows for the identification of the most effective and specific treatment options for each individual case \(^{(81)}\). Various forms of HT have been identified and categorized based on the relative cause or characteristics of the specific hypertensive case, where the most commonly encountered forms have been identified as primary and secondary HT.
Primary (Essential) Hypertension

HT can be of known or unknown causes. Primary HT (characterized by a sustained SBP ≥ 140 mmHg and a DBP ≥ 90 mmHg) is the most prominent form of HT, accounting for ~95% of the total cases (82). Although primary HT is commonly considered to have no identifiable cause, it is suspected to manifest through the interaction of an individuals’ inherited genetic traits and their exposure to certain behavioral, environmental and lifestyle-related “hypertensinogenic factors” (81-83). Hypertensinogenic factors are defined as a substance or situation that tends to increase BP and include obesity, insulin resistance, high alcohol or salt intake, aging, a sedentary lifestyle, excessive stress, low potassium intake, and/or low calcium intake (82;84;85).

Elevations in arterial stiffness (measured by the determination of arterial stiffness indices) have also been found in primary HT (86;87). Carotid arterial compliance (CAC) is one such index, representing the resistance provided by the walls of the carotid arteries against the pulsatile output of the heart (88). Reductions in CAC occur as a result of arterial wall structural reorganization in response to the prolonged exposure to elevations in BP (86), and have been found to be correlated with target organ damage in HT-related CVD (86). Reductions in CAC have been found to occur in concert with other CVD risk factors, including advanced aging (75;89;90), smoking (89), and physical inactivity (75), independent from the occurrence of HT. Therefore, reduced CAC can thusly i) contribute to the establishment or ii) be a consequence of elevated arterial BP (75). Furthermore, stiffer large arteries like the carotid artery are associated with the greater prevalence of isolated systolic HT in postmenopausal women, and may partially explain the acceleration in the rates of established postmenopausal CVD (88).

Although BP regulation is influenced by the previously described genetically
determined processes, it is currently unknown which genes cause BP to vary \(^{(82)}\).

Although an ideal genetic BP regulatory phenotype is known, countless phenotypic variants occur within the general population; inherited BP could range from low normal BP to severe HT \(^{(75)}\). Certain hypertensinogenic factors, such as obesity, excessive alcohol consumption, or insulin resistance also have important genetic components, and their interaction with the inherited control of BP may also influence BP regulation \(^{(82)}\). Furthermore, the interaction between genetics and environment factors can also result in the aberrant functioning of the regulatory processes that are in place to maintain arterial BP homeostasis, including sympathetic nerve activity, the RAAS, endothelial-derived factors, sodium excretion, vascular reactivity and cardiac contractility \(^{(82)}\). The combined contribution of these intermediary phenotypes determine an individuals’ TPR and \(Q\), and consequently \(BP\) \(^{(82)}\), where the interruption of the normal regulation of any of these processes can contribute to the establishment of HT.

A haemodynamic hallmark of primary HT is a persistent elevation of TPR that is thought to occur through pathological SNS overdrive \(^{(91)}\). Excessive SNS innervation can affect the heart, increasing both HR and cardiac contractile force, both of which contribute to pathological elevations in \(Q\) and sustained elevations of resting BP in HT \(^{(91)}\). Although excessive SNS activity has been identified in primary HT, the underlying cause of this elevation remains equivocal.

**Secondary (Systemic) Hypertension**

Secondary HT occurs as a result of an identifiable cause, such as reduced renal function or damage, pheochromocytoma, Cushing’s disease, certain cancers, or as an adverse reaction to certain types of illicit drugs or medications \(^{(14)}\). Although the number
of potential causes of secondary HT seems daunting, this condition only accounts for a small percentage of all HT cases, and commonly occurs as a co-morbidity to an identified pathology (81;83).

1.1.4.1 Cardiac Output and Total Peripheral Resistance in Hypertension

HT is consistently characterized by the dysfunctional regulation of Q, TPR, or both (81;83), suggesting that treatment and management options for HT should be aimed at regaining homeostasis between Q and TPR.

**Cardiac Output and Hypertension**

Increased Q has been found in some younger, borderline HT individuals (81). If the established HT is a result of increased Q, it can arise from one of two ways, i) from an increase in fluid volume within the vasculature (preload), or ii) from increased cardiac contractility via elevated cardiac neural stimulation (81). HT is associated with an increased sympathetic outflow and reduced PNS activity, which represent aberrant autonomic functioning and a reduced autonomic ability to modulate HR (92). The reduced vagal innervation of the heart can result in chronic elevations of resting HR, which would increase Q and contribute to sustained HT (93).

**Total Peripheral Resistance and Hypertension**

Dysfunctional modifications to sympathetic neural conductance contribute to the impaired regulation of TPR and have been consistently observed in individuals with clinically diagnosed HT. Several defining factors of the aberrant sympathetic responses that are characteristic of HT include impaired buffering capacity of baroreflex (94;95) and increased sympathetic nerve outflow/activation (95-97). With respect to the latter, SNS
over-activity has been implicated in early and sustained HT \(^{(81)}\). However, both of the implicated neurovascular mechanisms seem to play an important role in the impaired regulation of TPR in HT.

Multiple factors contribute to sustained elevations in TPR in HT, all of which primarily affect pre-capillary vessels with lumen diameters \(\leq 500 \mu m\) \(^{(98;99)}\). The increased stress placed on the arterial walls during sustained elevations in BP stimulates structural adaptations in these resistance vessels that are characterized by reduced arterial lumen diameter and an increased ratio of the vascular smooth muscle thickness (tunica media) to lumen diameter, referred to as the media-to-lumen ratio \(^{(81)}\). As previously mentioned in Section 1.1.2 Arterial Blood Pressure, Poiseuille’s law states that vascular resistance is positively related to both the length of the arterial system and the viscosity of the fluid medium within the system (i.e. blood), and negatively related to the fourth power of the arterial lumen diameter \(^{(15)}\). As neither blood viscosity nor arterial length is considerably altered with HT, any small changes in arterial lumen diameter can have a profound impact on vascular resistance \(^{(14;36;81)}\). The sustained elevation of TPR in HT most closely reflects the minute changes of vascular structure that result in reductions in arterial lumen diameter \(^{(100;101)}\).

Outward hypertrophic remodeling is characterized by increased media-to-lumen ratio that occurs as a result of the hypertrophy or hyperplasia of the vascular wall components and is also characteristic of sustained HT \(^{(102)}\). These structural adaptations increase the arterial cross-sectional area (CSA) and contribute to a loss in the elastic nature of the arteries \(^{(81;102)}\). Vascular remodeling is an alternative process that mediates a reduction in media-to-lumen ratio. This process is characterized by the rearrangement of existing vascular material is such a way that results in a reduction of the external arterial
diameter without modifications to the arterial CSA \(^{(81;98)}\). Vascular remodeling has been suggested as the primary vascular structural adaptation that occurs in response to sustained elevations in BP \(^{(81)}\).

### 1.1.4.2 Menopause and Hypertension

Menopause is a natural female phenomenon that involves the reduction in the production and concentration of circulating estrogen. This process coincides with the 6\(^{th}\) decade of a woman’s life, where a relationship between the onset of menopause and elevated CVD-risk has been identified and is well established \(^{(103)}\). Estrogen acts throughout the CVS in a protective manner through estrogen receptor activation and the subsequently stimulated inhibition of smooth muscle cell proliferation and fibrosis, attenuation of atherosclerotic plaque progression, and re-endothelialization of injured vasculature. All of which ultimately contribute to cardiovascular health in both men and women \(^{(103)}\). As women enter menopause and experience large reductions in estrogen production, the cardio-protective effects of estrogen are diminished, and as such, women who display higher SNS activity are more likely to develop HT \(^{(104)}\).

The prevalence of diagnosed HT in postmenopausal women exceeds that observed in age-matched men \(^{(105)}\), where sex-related differences in the neurovascular control of BP are suggested as the primary mediator in the observed difference \(^{(104;106)}\). In support of this notion, women display lower autonomic support of BP regulation \(^{(107)}\), with a concomitant blunted vasoconstrictor response \(^{(108)}\). For example, cardiovagal baroreflex sensitivity and the systemic vascular response to an autonomic challenge (e.g., tilt) is lower in HT women than in age-matched HT men \(^{(109;110)}\). Ancillary to aberrant autonomic regulation of BP in postmenopausal women, concurrent increases in arterial
stiffness and modifications to Q may also play a role in the amplified rate of established HT \(^{(88)}\), and may also contribute to the increased occurrence of cardiovascular complications in this population.

### 1.1.5 Recommendations for the Treatment of Hypertension

The traditional clinical objective when attempting to manage HT has been to obtain resting BP within the 140-160/90-100 mmHg range, but recent evidence suggests that lower BP \((\geq 120/80 \text{ mmHg})\) should be the optimal treatment goal \(^{(79)}\). As such, recently updated HT-management guidelines suggest attaining lower BP values \((<120/80 \text{ mmHg})\) in order to minimize the overall risk of CVD-related morbidity and mortality \(^{(80;111)}\).

#### 1.1.5.1 Lifestyle Modifications For Hypertension

Lifestyle modifications (dietary modifications, increasing physical activity levels) are the initial and most commonly suggested management options for HT \(^{(8;80;112;113)}\). Lifestyle modifications that solely depend upon the consumption of healthy nutritional meals and participation in physical activity have been shown to reduce resting BP to within normal range in many populations \(^{(8,80;112;113)}\). Further lifestyle modifications can also be employed in attempts to reduce an individuals’ exposure to other hypertensinogenic factors, including reducing dietary sodium intake, limiting alcohol consumption, maintaining a healthy body weight. Following the Dietary Approaches to Stop Hypertension (DASH) can also potentiate the hypotensive benefits achieved through the participation in regular physical activity \(^{(8;80;112;113)}\).

The DASH diet pertains to nutritional modifications that focus on the inclusion of a large amount of vegetables, fruits, and low-fat dairy products in the diets of persons
with or without HT \(^{114}\). Some individuals respond to the nutritional modifications of the DASH diet to a greater extent than others, but the potential of the DASH diet as a HT treatment option remains apparent, as those who do respond to the diet experience reductions in resting BP that mirror those that can be obtained through a single, pharmacological HT treatment \(^{80}\). The DASH diet has been found to be significantly associated with reductions in SBP regardless of sodium-intake, although the reductions became more pronounced in individuals on high-sodium diets compared to those on low-sodium diets \(^{84;114}\). A DASH diet with a concomitant reduction in sodium intake to what is currently considered low levels \((67 \pm 46 \text{ mmol/day})\) can produce reductions in mean SBP of up to 7 mmHg in NTs and 11 mmHg in HTs \(^{114}\). The observed reductions in resting BP following simple lifestyle modifications like following the DASH diet and reducing excessive sodium intake plays an integral role in the prevention and/or management of HT.

### 1.1.5.2 Pharmacotherapy for Hypertension

While lifestyle modifications have been shown as an effective management and prevention measure for HT, many individuals often require additional pharmacotherapy in order to reduce BP to target levels \(^{8;80;111}\). As previously mentioned BP is regulated through a myriad of neural, humoral and locally produced mechanisms, which suggests the potential for the intervention in the aberrant functioning of these mechanisms through pharmacological HT therapy. In morbidly progressed or resistant HT cases, more than one medication may be needed to adequately control BP \(^{80}\). Commonly prescribed anti-HT medications include diuretics, angiotensin converting enzyme inhibitors (ACEIs),
angiotensin receptor blockers (ARBs), beta-blockers (BBs) and calcium channel blockers (CCBs)\textsuperscript{(80)}.

**Diuretics**

Diuretics (thiazide or loop) are the recommended first-line pharmacological intervention for HT\textsuperscript{(80)} and both act to inhibit solute re-absorption (i.e. Na\textsuperscript{+}) from the renal tubules increases sodium excretion (natriuresis) and, through elevated osmotic drive, increases H\textsubscript{2}O excretion and urinary output (diuresis)\textsuperscript{(14)}. Although the increased urinary output and fluid removal occurs secondary to the inhibition of renal tubular sodium re-absorption, the overall effect results in reductions in total blood volume and arterial BP\textsuperscript{(14;45)}.

**Angiotensin-Converting Enzyme Inhibitors**

As previously described, the conversion of angiotensin I to angiotensin II is dependent upon the action of the angiotensin converting enzyme. The ACEI-mediated inhibition of this process reduces the production of the vasoconstrictor angiotensin II and thereby reduces the vascular tone and, therefore, effectively lowers BP\textsuperscript{(14;83)}. The ACEI-mediated reduction in circulating angiotensin II and the concomitant reduced arterial BP is translated to reductions in renal pressure and glomerular filtration rate which increases sodium and H\textsubscript{2}O excretion rate and reduced total blood volume\textsuperscript{(14)}. These ACEI actions provide the basis for the chronic BP reductions that are required to treat and manage HT\textsuperscript{(14)}.

**Angiotensin II Receptor Blockers**

ARBs are competitive antagonists for the angiotensin II receptors, acting to reduce
angiotensin II receptor activation and the subsequent vasoconstrictive effects that are initiated as a result of this binding \(^{(14;83)}\) which contributes to reductions in TPR and facilitates reductions in BP \(^{(14)}\). ARBs also inhibit renal ionic re-absorption and aldosterone secretion, thus increasing fluid excretion, reducing total fluid volume and blood volume and thereby contributing to reductions in BP \(^{(14;83)}\).

**Beta-Blockers**

BBs are competitive antagonists at the sympathetic ß-adrenergic receptors of the heart and vasculature \(^{(14)}\) which act to reduce the work of the heart by preventing the sympathetic enhancement of heart rate, cardiac metabolism and vascular tone \(^{(14;83)}\). The combined effect of BBs on cardiac functioning results in the reduction in both Q and TPR, which mediates reductions in BP \(^{(14;83)}\).

**Calcium Ion Channel Blockers**

The CCB utilized for BP management are classified as dihydropyridine CCBs, which effectively block membrane-bound voltage-gated \(Ca^{2+}\) channels in cardiac and vascular smooth muscle to impede the voltage-dependent transit of \(Ca^{2+}\) ions across cellular membranes and thereby inhibit the \(Ca^{2+}\)-dependent initiation of VSMC contraction \(^{(115)}\). The reduction of the contractile tone of the VSMC results in reductions in TPR, and thus decreased BP \(^{(14;83)}\).

**Effectiveness of Pharmacotherapy in Hypertension Management**

In 2008, Canadians spent an estimated $28 billion dollars on pharmaceuticals, with approximately 20% of the spending focused on hypertensive medications \(^{(116;117)}\). However, the use of pharmacological interventions for HT treatment has been found to be
effective in less than 50% of treated patients\textsuperscript{(118)}. Furthermore, pharmacologically-mediated reductions in BP to levels that are within the normal range remains elusive to a vast majority (~85%), and the use of pharmacology as an adjunct-treatment has less success in managing elevated BP in older women than their age-matched male counterparts\textsuperscript{(119)}. Results from the Framingham Heart Study suggest that ~72% of treated individuals over the age of 60 are not able to attain target BP values through pharmacological interventions alone\textsuperscript{(120)}. In addition, evidence suggests that medicated individuals who have attained adequate BP control may still exhibit elevations in sympathetic outflow\textsuperscript{(121)}. This persistent elevation in SNS activity may explain the high rates of morbidity and mortality among individuals medicated for HT\textsuperscript{(121)}, despite clinically significant, pharmacologically-mediated reductions in arterial BP.

1.2 Exercise and Hypertension

Physical activity can reduce resting BP, and as such, chronic exercise has become an integral component of HT management and prevention programs\textsuperscript{(9,13)}. The American College of Sports Medicine has developed HT-based exercise recommendations, suggesting that HT individuals participate in moderate intensity aerobic exercise ($40 \leq 60\%$ of an individual’s heart rate reserve) for 30 to 60 minutes a day, between 3 to 7 times per week in order to garner the associated health benefits\textsuperscript{(9)}. Resistance training (RT) is recommended as an adjunct treatment, to be performed, 2 to 3 times per week at an intensity that would allow for 12 to 15 repetitions per exercise, for every major muscle group\textsuperscript{(8)}. Currently there are no endorsed exercise guidelines for isometric exercise training.
1.2.1 The Effects of Exercise Training on Arterial Blood Pressure

Endurance (Aerobic) Exercise Training

A collection of meta-analyses collectively confirm the ability of chronic aerobic training (AT) to reduce resting BP in HT and in those with normal arterial BP, regardless of the exercise modality (i.e. walking, running, cycling), intensity (30 to 90% VO_{2max}), frequency (1 to 7 days per week), or duration (30 to 60 minutes per day) \(^{(8)}\). The age of the participants enrolled in these studies ranged from 18 to 79 years (median ~ 45 years), implicating the ability to experience aerobically-induced reductions in resting BP throughout the lifespan \(^{(8)}\). Furthermore, HT individuals consistently experience more dramatic reductions in resting BP following AT (HT: ~7/6 mmHg; NT: ~2/2 mmHg) \(^{(65)}\).

To determine the effects of training-induced modifications to Q versus TPR and their relative contributions to the training induced reductions in resting BP, work by Spina \textit{et al.} \(^{(122)}\) focused on the cardiac functional adaptations to AT in a healthy, elderly population (N=31; 16 females, 64 ± 3 years). Sex-based differences in the cardiovascular adaptations to training were observed, where training-induced improvements in resting Q (as determined by elevations in SV) occurred in the male participants only, while improvements within the female participants were the result of enhanced arterial-venous O\(_2\) extraction \(^{(122)}\). As such, reductions in resting Q are not typically expected in women with above normal BP following exercise training. These observations implicate reduced TPR as the primary mechanism that is responsible for reductions in resting BP in this population \(^{(8)}\).

Reductions in TPR are likely mediated through vascular changes (i.e. increased endothelial-dependent vasodilation), arterial structural changes (i.e. increased CSA of the
resistance arterioles), and/or functional changes (i.e. NE receptor desensitization and increased NO availability and release). Neurological modifications (reduced sympathetic nerve activity) and genetics may also be implicated in the physiological adaptations to AT (8).

**Dynamic Strength (Resistance) Training**

Resistance exercises involve controlled concentric and eccentric movements, where muscles are shortened (concentric) or elongated (eccentric) while under tension and produce contractions that change the angle of the joints throughout the activity (123). Historically, the effects of RT on resting BP has been equivocal, however, two recent meta-analyses (N=≥320 male and female NT and HT subjects; 182 exercise, 138 control) found statistically significant reductions of ~3 mmHg for both SBP and DBP following chronic RT (124;125). Although this reduction may seem modest from a clinical standpoint, reductions of 3 mmHg among the average population has been estimated to mediate a significant reduction in the occurrence of severe CVD-related events and all-cause mortality (126;127).

The mechanism(s) responsible for the reduction in arterial BP that is provided by RT are similar to those seen with AT, where vascular, structural, functional and/or neurohumoral adaptations have been implicated in the exercise-induced reductions of TPR (8).

**Isometric Handgrip Training**

Isometric exercises incorporate the generation of muscular force without changing the length of the exercising muscle (128). Over the last decade, isometric handgrip training (IHG; a novel form of exercise training where participants perform multiple, timed,
sustained contractions on a programmed handgrip dynamometer, performed at a set percentage of their maximal effort (MVC) for up to 10 weeks) has received attention in the literature for its positive effects on resting BP among healthy and clinical populations. For example, Wiley et al. (129) employed a randomized controlled, IHG-training protocol, (4, 2 minute isometric contractions at 30% of their MVC, where each contraction is separated by 3 minutes of rest, 3 times per week for 8 weeks) and observed average reductions in resting SBP and DBP that reached ~13 and 15 mmHg, respectively. A second protocol, with a slightly modified IHG-training protocol (4, 45 second contractions at 50% MVC, separated by 1 minute of rest, 5 times per week for 5 weeks) was employed and produced statistically significant reductions in resting SBP and DBP of ~10 and 9 mmHg, respectively.

Ray and Carrasco (130) examined the effects of 4, 2 minutes IHG contractions held at 30% MVC, performed 4 times per week for 5 weeks in NT adults (N=17; 19 – 35 years, 46% women), reporting reductions of ~5 mmHg for resting DBP, while observing no statistically significant reductions in resting SBP (~3 mmHg). More recently, the effects of IHG training on arterial BP in NT individuals (N=13; 27.5 ± 14.2 years, 23% women) was further investigated by McGowan and colleagues (131), where an 8 week unilateral IHG protocol (consisting of 4, 2 minute IHG contractions at 30% MVC using the non-dominant hand, separated by a 4 minute rest period between contractions) was employed. Similar reductions in resting BP (~5mmHg SBP) were observed using this modified isometric exercise protocol.

In 2008, Millar and colleagues (132) provided further evidence of the BP lowering effects of IHG training in an older, NT population (N=49; 66.4 ± 0.9 years; 57% women). Through the use of an 8 week bilateral IHG training protocol (as previously described),
reductions in both SBP and DBP of 10 mmHg and 3 mmHg, respectively, were observed. Of particular interest, females responded with greater reductions in BP than did their male counterparts (female slope coefficient = -0.55 vs. male slope coefficient = -0.20, p<0.01) and the training effects appeared to be most pronounced among the older participants (132).

In 2003, the clinical effectiveness of IHG training was explored in HT individuals (N=17; 41% women) using a 10 week bilateral IHG training protocol (as previously described). The IHG training produced significant reductions in both SBP and DBP (19 mmHg and 7 mmHg, respectively) in this HT population (92).

In 2007, McGowan and colleagues (133) examined and compared the effects of an 8 week bilateral and unilateral (as previously described) IHG training program in individuals medicated for HT (N=16; 25% women). SBP was reduced by ~15 mmHg and ~9 mmHg for the bilateral and unilateral protocols, respectively (133). These results provide additional evidence of the effectiveness of IHG training as a management option for HT (92). In the same year, a multilevel analysis investigated the effects of IHG training in medicated HT (118), finding combined reductions of ~6 mmHg and ~3.0 mmHg for SBP and DBP, respectively (118), which solidified the use of this exercise modality as an effective exercise management option for those with HT.

This collective work was recently extended by Stiller-Moldovan et al. (2012) who observed clinically-relevant (8) reductions in 24-hour ambulatory BP in well-controlled, medicated hypertensives following IHG training (N=11 IHG training group, N=9 control group; 50% females).

Although there is much data to support the effectiveness of IHG training in reducing resting BP, the mechanisms responsible for this reduction remain equivocal. Potential mechanisms responsible for reduced vascular resistance following exercise

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training have been suggested and are thought to be the result of neurohumoral and/or structural adaptations within the CVS. Improvements in the neurohumoral regulation of TPR that would mediate reductions in resting BP include reduced SNS innervation to the vasculature and/or improved local vasodilator influence on the VSMC (i.e. NO), while increased arterial lumen diameter (which would increase arterial radius and thus reduce resistance to blood flow and hence arterial BP) and/or reduced arterial stiffness (by means of improved arterial compliance) have been hypothesized as the potential structural vascular adaptations to training that would permit reductions in TPR and subsequently, BP (133).

1.3 Arterial Stiffness

Increased central arterial stiffness is a cornerstone of the aging process and occurs as a result of many chronic diseases, such as diabetes, atherosclerosis and renal failure (134). Arterial stiffening is also correlated with increased CVD risk, myocardial infarction, heart failure and cardiovascular-related mortality (135). Clinical surrogate markers of vascular stiffness, including elevations in PP and isolated systolic HT also increase with age and these associated conditions (80). Arterial stiffness alters both resting and stress-induced haemodynamics and energy expenditure within the CVS. The effect of this stiffening predisposes an individual to the previously mentioned CVDs, lowers the symptom threshold, contributes to orthostatic hypotension and increases perception of dyspnea upon exertion in older adults (134).

1.3.1 Structural Components of Arterial Stiffening

The stability, resilience, and elasticity of the arterial system depend upon the two major extracellular matrix (ECM) scaffolding proteins: collagen and elastin, while others
such as fibronectin and proteoglycans provide additional structural support \(^{(134)}\). Collagen provides structural integrity, while elastin promotes elasticity and distensibility.

The production and degradation of collagen and elastin within the ECM is regulated by activated serine proteases and matrix metalloproteases (MMPs) \(^{(136)}\), which are grouped as collagenases, elastases or gelatinases \(^{(137)}\). The MMP regulated degradation of collagen and elastin within the ECM results in the production of broken and frayed collagen and elastin molecules, which reduces vascular elasticity and increases arterial stiffness \(^{(138;139)}\). Arterial stiffening is further enhanced through the degradatory and inflammatory processes that occur within the ECM following gelatinase activation \(^{(116)}\) via an inflammatory-mediated dysregulation of MMP homeostasis that results in the overproduction of abnormal collagen, reduction in normal elastin and contributes to increases in arterial stiffening \(^{(140)}\). Furthermore, the deposition of additional structural components within the ECM, including chondroitin sulfate, heparin sulphate, proteoglycans, and fibronectin can also contribute to elevations in arterial ECM thickness and stiffness with age \(^{(141)}\).

### 1.3.2 Pathophysiology of Arterial Stiffening

Arterial stiffening develops as a result of the complex interaction between stable and dynamic modifications of the vascular wall that involves both structural and cellular components of the arterial system \(^{(134)}\) \((\text{Figure 10; page 120})\). The arterial ECM structural organization is influenced by haemodynamic forces within the CVS and circulating compounds, such as circulating hormones, sodium chloride, glucose, and insulin \(^{(49)}\). Furthermore, it is important to note that arterial stiffening is not uniformly distributed through the arterial tree, but rather has been found to occur in isolated patches.
where the stiffened arterial segments are most often observed in the central conduit arteries, like the carotid artery \(^{86}\). The aging process or conditions like HT can augment the vascular changes that occur with arterial stiffening and accelerate the pathogenic progression of the diseased state \(^{143;144}\). While increases in intimal-media thickening (IMT) and stiffening of the vasculature are hallmark characteristics of arterial aging, increased central arterial lumen diameters have also been observed \(^{144}\). These increases are thought to occur as a compensatory mechanism, where the arterial system is structurally modified in response to increases in IMT in an attempt to maintain adequate haemodynamics within the CVS \(^{90;135}\). However, the effect of arterial stiffening with aging on BP is not often overcome exclusively through this process \(^{86;145}\).

**Lipids and Arterial Stiffening**

The relative degree that lipids contribute to arterial stiffening remains unclear. Lipids have been implicated as both a beneficial \(^{136}\) and negative \(^{139}\) influence of arterial ECM and wall composition, both of which depend upon the examined location within the arterial tree. Although the pathophysiology of atherosclerosis and arterial stiffening occur as a result of similar inflammatory, protease and oxidase-mediated stress-remodeling processes, causality remains unclear as both pathologies are commonly concurrently encountered \(^{134}\).

**Cellular Role In Arterial Stiffening**

Arterial stiffness can also be affected by endothelial functioning and VSMC tone. The tonic state of the VSMC can be modified via a myriad of factors, ranging from the mechanostimualtory influence that occurs as a result of modified Ca\(^{2+}\) ion flux within the cells due to cellular stretch that accompanies VSMC contraction, and/or in response to
circulating or locally produced vasoactive substances, such as angiotensin II, endothelin-1, transforming growth factor beta (TGF-β), reactive oxygen species (ROS), and NO \(^{(134)}\). Endothelial dysfunction relates to the inability of the endothelium to respond to circulating vasoactive substances and/or initiate the production of endothelium-derived vasodilatory (i.e. NO) or vasoconstrictive (i.e. endothelin-1) substances \(^{(146)}\). Endothelial dysfunction emanates, in part, from an imbalance between the circulating vasodilatory and vasoconstrictive substances within the vasculature \(^{(147)}\), where NO expression may be reduced \(^{(148)}\), and/or its production and release may be diminished as a result of the elevated expression of an endogenous NO synthase inhibitor (asymmetrical dimethylarginine; ADMA), activation of ROS via stress, hormones and their subsequent effects on the endothelium \(^{(149)}\). Most notably, plasma ADMA concentrations are positively correlated with carotid arterial IMT \((F = 11.1, p = 0.03)\), implicating aberrant ADMA regulation with the occurrence of increased arterial stiffness and other CVD risk factors \(^{(150)}\).

Furthermore, recent work by Peng \textit{et al.} \(^{(151)}\) highlights a positive feedback mechanism in place within the vasculature that acts to potentiate arterial stiffening and endothelial dysfunction, where the normal shear stress-stimulated endothelial NO production is significantly reduced when endothelial cells are exposed to realistic pulsatile perfusion after being mounted to a less distensible, more stiff silastic tubing model. The observations suggest that the ability of the arterial wall to stretch impacts endothelial mechanotransduction and functioning to a greater degree than a flow-mediated, pulsatile stimulus \(^{(151)}\), and the lack thereof contributes to the exacerbation of arterial stiffening.
Transforming Growth Factor Beta

TGF-ß has been identified as one of the primary cytokine released at the site of local tissue damage or chronic inflammatory situations that are responsible for the regulation of the initiation and termination of tissue repair processes (152). TGF-ß exists in three isoforms (TGF-ß₁, TGF-ß₂, and TGF-ß₃) and binds to its specific VSMC and fibroblast cell surface receptors (TGF-ß type I (TßRI) and type II (TßRII) receptors) (152). Aberrant regulation of TGF-ß underlies the development of local inflammation (eg., TGF-ß acts as a chemokine for leukocyte and fibroblast recruitment) (152) and the subsequent tissue fibrosis (via inhibition of MMPs and elevated expression of ECM proteoglycans, fibronectin and collagen) that is characteristic of countless disorders (152) and is associated with arterial stiffening in aging (153).

Neuroendocrine Role in Arterial Stiffening

The RAAS plays crucial role in the regulation of total fluid volume and arterial BP, however, it is also an important regulatory mechanism that can influence the adaptive responses of the CVS to BP abnormalities as well. Activation of the RAAS results in modifications of the ECM composition within the CVS by stimulating the expansion of the matrix and increasing fibrosis (154). The RAAS-driven fibrosis is characterized by increased inflammatory cells recruitment and the activation of the redox-sensitive NF-κB pathway within the vasculature (155). This pathway results in the modulation of local gene expression to favor the promotion of elevated hyperplasia while reducing cellular senescence, all of which have been found to contribute to arterial stiffening (155). The RAAS also contributes to arterial stiffening via angiotensin II, as angiotensin II-mediated production of ROS and the subsequent endothelial NO synthase enzyme uncoupling also
contributes to the endothelial dysfunction that occurs with arterial stiffening and HT\(^{(156)}\). This process can also activate the NF-κB pathway, potentiating the aberrant structural organization that occurs with arterial stiffening\(^{(157)}\). Angiotensin II can also directly affect arterial structural organization by promoting reduced elastin synthesis, initiating collagen formation and stimulating ECM remodeling and vascular hypertrophy\(^{(158;159)}\).

Aldosterone of the RAAS promotes vascular stiffness through the stimulation of VSMC hypertrophy and fibrosis by stimulating increased production and deposition of fibronectin within ECM\(^{(160)}\). Circulating concentrations of aldosterone are also closely linked to that of endothelin-1, where infusions of aldosterone increase ET\(_1\) production in murine models\(^{(161)}\). This relationship is important to consider, as ET\(_1\) produces vasoconstrictive and fibrotic effects within the vasculature through processes that are independent of aldosterone\(^{(161)}\) and suggests that there is a compounding effect of aldosterone and ET\(_1\) on the CVS that occurs in concert and contributes to the progression of arterial stiffening. Lastly, excessive tissue RAAS activity occurring in response to defects in the sodium-modulated tissue responses of the renal and adrenal systems also contributes to increased vascular tone, arterial stiffness, and other pathologic angiotensin II-like dysfunctions in local tissues in HT\(^{(162)}\).

**Genetic Role in Arterial Stiffening**

A number of genetic polymorphisms are associated with elevated arterial stiffening, including those within the ACE or angiotensin type I receptors\(^{(175)}\), ET\(_1\) A and B receptors\(^{(180)}\), collagen type-I\(_\alpha\)\(^1\)\(^{(181)}\), fibrillin-1 and IGF-1\(^{(182)}\) loci. However, these polymorphisms have only been noted in small scale studies using participants from specific ethnic populations and have yet to be identified in the general population.
1.3.3 Methods of Measuring Arterial Stiffness

Several predictive and direct, non-invasive methods have been developed for the evaluation of arterial stiffness at a variety of sites throughout the arterial tree. These methods involve the determination of arterial stiffness indices that are used to describe the structural organization, mechanical properties and functioning of the vasculature. The stiffness indices include the β-stiffness index, pressure-strain elastic modulus (Ep), distensibility co-efficient (DC), augmentation index (AIx), and arterial compliance.

β-Stiffness

β-stiffness is one of the most commonly employed clinical markers of atherosclerosis and arterial stiffening (163). β-stiffness is a unit-less index used for the assessment of arterial viscoelasticity as the mathematical formula used for it derivation adjusts the index for the distending pressure within the arteries (164). β-stiffness is determined following the measurement of arterial diameters and PP through the cardiac cycle according to the following formula: $\beta = \ln(P_s/P_d)/(D_s - D_d)/D_d$, where $ln$ is the natural logarithm, $P_s$ is the systolic arterial BP, $P_d$ is the diastolic arterial BP, $D_s$ is the maximal arterial diameter at peak systole, and $D_d$ is the minimum arterial diameter at peak end diastole (165). Higher values of β indicate arterial stiffening (165). As a measure of arterial stiffness, β is less pressure-dependent than others (i.e. Ep) and is therefore more reliable and reproducible (165).

Pressure-Strain Elastic Modulus

The Ep is a measure of arterial stiffness that is based on the relationship between stress and strain within the circulatory system (166). Stress is a measure of how strong a
material is [i.e. how much external force are the internal forces of a material able to withstand without succumbing to physical deformation or destruction\(^{(166)}\)], and can be mathematically determined by the formula: \( \sigma = \frac{F}{A} \), where \( \sigma \) is stress (N/m\(^2\) or Pa), \( F \) is the force applied (N), and \( A \) is the CSA of the material (mm\(^2\) or cm\(^2\))\(^{(166)}\). Strain describes the relative stretch of a material or object in response to elevations in external or internal forces\(^{(166)}\), and can be mathematically determined by the formula: \( \varepsilon = \frac{\Delta l}{l_0} \), where \( \varepsilon \) is strain (unitless), \( \Delta l \) is the extension of the length of an object following the exposure to an external force, and \( l_0 \) is the original length of the object before the external stress was applied\(^{(166)}\).

Ep is used to describe the extent to which a material will stretch (i.e. how much strain will be experienced) as a result of being exposed to a given amount of external force (i.e. stress)\(^{(165)}\). Ep is determined by the following formula: \( EP = \frac{P_s - P_d}{D_s - D_d}/D_d \), where \( P_s \) is the systolic arterial BP, \( P_d \) is the diastolic arterial BP, \( D_s \) is the maximal arterial diameter at peak systole, and \( D_d \) is the minimum arterial diameter at peak end diastole\(^{(165)}\). Higher values for Ep indicate reduced arterial elasticity\(^{(165)}\). As the derivation of Ep relies on the differences between SBP and DBP, the accuracy of this technique is highly dependent upon an accurate assessment of arterial BP\(^{(165)}\).

**Distensibility Co-efficient**  
Distensibility describes the ability of a material to expand or stretch in response to an applied force\(^{(167)}\). Within the CVS, distensibility is used to describe the ability of an artery to stretch in response to the pulsatile output of the heart. DC represents the stress on the arterial wall through the relationship between the relative changes in the CSA of an artery per unit pressure\(^{(187)}\) and is determined using the following formula: \( DC = \)
\[ \pi (D_s/2)^2 - \pi (D_d/2)^2 / \pi (D_d/2)^2 / \Delta P, \] where \( D_s \) is the maximal arterial diameter at peak systole, \( D_d \) is the minimum arterial diameter at peak end diastole, and \( \Delta P \) is the local pulse pressure \(^{(74)}\). Lower values for DC reflect reduced arterial distensibility and elevated arterial stiffness \(^{(168)}\).

**Augmentation Index**

The AI\(_x\) describes the degree that BP is augmented by the arterial system \(^{(165)}\). The AI\(_x\) is determined via applanation tonometry and the subsequent analysis of the PP waveform for the calculation of the difference between the maximal arterial pressure and that at the inflection point of the same wave \(^{(165)}\). This difference is used to determine AI\(_x\) using the following formula: \( \text{AI}_x = (\Delta P/PP) \times 100 \), where \( \Delta P \) is the difference between peak SBP and the inflection point of the arterial pressure waveform, and \( PP \) is the arterial pulse pressure \(^{(165)}\). AI\(_x\) is expressed as a percentage of arterial PP and describes the degree that the central aortic pressure is augmented by the reflected pulse wave \(^{(165)}\). AI\(_x\) values are negative in individuals where the velocity of the reflected pulse-wave is low (i.e. children) and positive when the velocity of the reflected wave is high (i.e. the elderly) \(^{(165)}\), where elevations in AI\(_x\) are associated with an elevated cardiovascular risk \(^{(169)}\).

**1.4 Arterial Compliance**

Arterial compliance is defined as the change in the CSA (\( \Delta A \)) of an artery per unit of pressure (\( \Delta P \)) \(^{(71;164;165)}\), and is a quantitative and qualitative assessment of the viscoelastic properties of the arterial wall \(^{(71)}\). Arterial compliance reflects the ability of the large central and peripheral conduit arteries to buffer the pulsatile output of the heart \(^{(164)}\). During systole, the elasticity of the central arteries (i.e. aorta, carotid) reduces left
ventricular wall stress by buffering the rise in peak systolic pressure\(^{(170)}\). During diastole, the stored energy is thusly released and facilitates organ perfusion throughout the cardiac cycle\(^{(170)}\). The relative diameter change of the artery from its maximum at peak systole to its minimum at diastole reflects the compliance of the artery\(^{(171)}\). Under normal circumstances arterial elongation during systole is negligible\(^{(168)}\), allowing for the assumption that an increase in the volume of an arterial segment is exclusively the result of increased arterial diameter\(^{(171)}\). Thus, arterial compliance can be determined based on the variation in the CSA and BP within an artery throughout the cardiac cycle\(^{(168;171)}\). This definition suggests that any modifications to either the arterial CSA or the pressure exhibited therein will affect arterial compliance (or stiffness). Elevations in PP provide a stimulus that will increase arterial stiffness\(^{(86;172)}\) and have been found to be an independent risk factor for CVD\(^{(173;174)}\). The conservation of large artery compliance is essential for the dissipation of arterial PP, and provides the capillary beds with the appropriate pressure to allow for normal fluid exchange with the extra-vascular environment while preserving the structural integrity of the fragile capillary walls\(^{(102)}\).

The curvature of the PP waveform is influenced by the interaction of left ventricular mechanics with the systemic arterial system, which allows for the reflection of this waveform to be used to describe many features of the pressure and flow mechanics within the CVS\(^{(175)}\). The intensity of the pulse wave reflection contributes to the establishment of a number of cardiovascular pathologies, including reductions in arterial compliance\(^{(102;171;176)}\). In HT, the structural adaptations that occur within the vasculature result in reductions in vascular lumen diameter and intima-medial thickening, all of which contribute to the loss arterial elasticity and increases in PP and thereby reduce arterial compliance and exacerbate the arterial stiffening process\(^{(102;171;176)}\).
1.4.1 Assessment of Arterial Compliance

Arterial compliance can be evaluated three ways: i) systemically (observing the ratio of PP to SV), ii) regional or segmentally (indirectly using pulse-wave velocity (PWV = distance (m) / transit time (sec) over the arterial segment)), or iii) locally (ΔA/ΔP) (71).

Systemic Arterial Compliance

The method used to determine systemic arterial compliance estimates arterial elasticity throughout the systemic circulation through the use of the ‘area method’ (177), which is performed by placing a hand-held Doppler flow velocimeter over the suprasternal notch at the base of the neck to estimate ascending aortic blood flow while concurrently performing applanation tonometry to estimate the aortic PP (177). Systemic arterial compliance is then calculated according to the formula: SAC = Ad/R(ΔP), where R is an estimate of TPR (derived as MAP/mean ascending aortic blood flow), Ad is the area under the diastolic pulse pressure waveform, and ΔP is the aortic PP (177). This method determines systemic compliance based on estimates provided from models of the circulation (87), and thus, has been considered a rather crude approximation that does not provide the means for the accurate evaluation of arterial elasticity (71;87).

Regional or Segmental Arterial Compliance

Regional or segmental arterial stiffness is indirectly determined by measuring PWV over a certain arterial segment (71). PWV in different regions can be measured using a variety of instruments, including the Complior (Colson, Paris, France), the Wall Track System (Pie Medical, Maastricht, Netherlands), the SphygmoCor (PWV Medical Pty Ltd., Sydney, Australia) and other customized devices. PWV is calculated using the
formula:  \( PWV = \frac{\text{distance}}{\text{transit time}} \), where \( \text{distance} \) is the physical measured distance between the two pressure transducers on the selected arterial segment, and \( \text{transit time} \) represents the time delay between the feet of the proximal and distal PP waves.  

The Complior is a semi-automated device that uses pressure transducers to determine the beat-to-beat time-delay between PP waves at two ends of an arterial segment. When the distance between the transducers is entered into the device, PWV is automatically determined and reported as the mean of 10 consecutive pressure waveforms. As the Complior allows for the simultaneous acquisition of the arterial PP waves from two arterial sites, it is assumed to be the most accurate technique to determine regional arterial PWV. The SphygmoCor and Wall Track System measure the time-delay between the R-wave of the electrocardiogram (ECG) and the feet of the pressure and distension waveforms within specific arterial segments. Similar to the Complior, PWV is calculated using the SphygmoCor and Wall Track System by determining the transit time between the PP waves at two ends of an arterial segment and the distance between the transducers. However, the latter techniques hold several benefits over others, as they do not require hand-held applanation tonometry for PP determination (instead, the pressure transducers are fixed over the desired locations using Velcro straps) and require very little training time (a few days to weeks) for new investigators to obtain reproducible measurements.

PWV is also inversely related to the arterial DC, and as such, can be indirectly determined via the Bramwell-Hill formula: \( PWV = \frac{1}{\sqrt{\rho \times DC}} \), where \( \rho \) represents the density of the blood and \( DC \) represents the distensibility coefficient.

A major limitation to these techniques lies within the ability to accurately measure
the appropriate distance for its inclusion in the PWV calculation. Distance can be estimated with accuracy through the direct measurement between the two pressure transducers in situations where a relatively straight arterial segment is being measured (i.e. the brachial-radial arterial segment\(^{(71)}\)). However, the distance measurement/estimation becomes a major limitation when the measured arterial segments are not straight or if the proximal and distal pulse waves are recorded from different arterial axis sites, as the pulse waves propagate in opposite directions at these locations (i.e. the carotid-femoral segment\(^{(71)}\)). The identification of the foot of the pressure wave may also prove problematic during data analysis, where accuracy primarily depends on the sampling rate employed and the technical skills of the investigator performing the measurements\(^{(71)}\).

**Local Arterial Compliance**

The local arterial compliance is defined as the compliance of a given artery per unit of length, representing the change in the CSA of the artery per unit of pressure\(^{(71)}\).

Arterial dimensions are commonly measured using ultrasonography and/or echo-tracking techniques (NIUS02 and WTS), while PP is determined using applanation tonometry\(^{(74;75;88;164;180;181)}\).

CAC is a local, non-invasive assessment of carotid arterial compliance, which describes the ability of the carotid arteries to buffer the pulsatile output of the heart\(^{(204)}\).

Carotid arterial diameters are commonly obtained from the left carotid artery via B-mode ultrasonography while PP waveforms are obtained from the right common carotid\(^{(74)}\). The arterial diameters are then measured leading-edge to leading-edge\(^{(74;182-184)}\) with a high resolution linear transducer that is placed longitudinal to the artery, 1-2 cm proximal.
to the carotid bulb \(^{(74;75;164;180;181;183)}\). After which, continuous digital recordings of arterial diameter and PP fluctuations are obtained for at least two cardiac cycles for offline analysis \(^{(74)}\). Local arterial compliance is then calculated using the following equation: 

\[
CAC = \frac{\pi(D_{\text{max}}/2)^2 - \pi(D_{\text{min}}/2)^2}{\Delta P},
\]

where \(\Delta D\) is the change in arterial diameter from systole \(D_{\text{max}}\) to diastole \(D_{\text{min}}\), and \(\Delta P\) is the arterial PP \(^{(74;164;180;181)}\). CAC measured within older female populations has been observed to range from 0.04-0.14 mm\(^2\)/mmHg \(^{(181;185;186)}\).

Several limitations to this technique exist, primarily concerning the accurate determination of PP. Although applanation tonometry is considered more accurate and appropriate than the Finapres for PP determination, this technique has also been found to overestimate PP in certain situations, where some investigators have reported unreliable magnitudes in the tonometrically-obtained PP \(^{(187)}\). Furthermore, the calibration of the tonometer to a PP determined from a reference artery (i.e. the brachial artery) is important to maintain the accuracy of the instrument \(^{(71)}\). This practice is based on the observation that the MAP is constant and that DBP does not substantially change throughout the arterial tree \(^{(170)}\). Following calibration, applanation tonometry is performed at the target and reference arterial sites to verify the calibrated accuracy \(^{(71)}\), and to ensure a reliable PP is obtained for the calculation of CAC.

### 1.4.2 Reduced Arterial Compliance and Hypertension

The elastic nature of the arteries is diminished as stiffening progresses to the point where the central arteries are no longer able to effectively buffer the pulsatile output of the heart, resulting in the progressive elevation of SBP and reduction in DBP \(^{(188)}\). The pathologic elevation of SBP facilitates a rise in left ventricular workload \(^{(189)}\) (initiating
left ventricular hypertrophy), while the reduction in DBP impairs coronary perfusion\(^{(190)}\).

A cyclic relationship is soon developed as both of these processes place unfavorable stress on the CVS and contribute to sustained stiffness-related elevations in arterial BP\(^{(188)}\).

Reduced CAC is characteristic of HT, where sustained elevations of MAP and PP stimulate increases in arterial wall thickness\(^{(182)}\) in an attempt to mediate the normalization of arterial wall stress\(^{(191)}\), and could potentiate the development of atherosclerosis in these populations\(^{(192)}\). Stiffer large arteries like the carotid artery are associated with the greater prevalence of isolated systolic HT in postmenopausal women and may partially explain the accelerated rates of established CVD within this population\(^{(88)}\). Although elevations in BP contribute to arterial stiffening, the intrinsic effect of aging on the vasculature also poses an independent threat to cardiovascular health, where reductions in compliance from normal values can span between 25% and 45%, depending upon the individuals’ level of habitual exercise participation\(^{(75)}\), or the use of hormone-replacement therapy (HRT)\(^{(164)}\).

1.4.3 Treatment Recommendations for Reduced Arterial Compliance

Several management options for arterial stiffening have been identified, and as in HT-management, the treatments available are primarily associated with the use of pharmacotherapy BP in combination with various lifestyle modifications (i.e. reductions in dietary salt intake\(^{(193)}\) and increasing physical activity levels).

**Pharmacotherapy for Reduced Arterial Compliance**

Pharmacological treatments to reduce arterial stiffening include those that are directly aimed at modifying the structure (e.g., nitrates) or those involved with modifying
the physiological stresses within the arterial system via reductions in BP (e.g., angiotensin II and aldosterone antagonists\(^{194,195}\)).

### 1.5 Effects of Exercise Training on Arterial Compliance

**Endurance (Aerobic) Exercise Training**

Aerobic exercise has long been considered an effective intervention method for arterial stiffening \(^{134}\). During AT, the continuous elevated pulsatile output from the heart occurs at the appropriate intensity to stimulate modifications to the structural organization of the arterial wall by promoting elevated arterial distensibility, compliance and reduced stiffness \(^{134}\). However, the majority of the available literature focuses on the effects of AT on arterial stiffening in males, where AT has consistently shown to produce significant reductions in aortic PWV, AI\(_x\), and CAC in this population \(^{196}\).

Although women have been underrepresented within the literature, recent evidence suggests that AT may be able to manage arterial stiffening in females as well. For example, Moreau *et al.* \(^{164}\) investigated the effects of regular aerobic exercise, HRT, and their influence on CAC in three groups of healthy, postmenopausal women using a combination of cross-sectional (N=69; personal preference of exercise) and intervention (N=12; walking intervention) studies. In the cross-sectional study, 69 participants were segregated into three groups; 20 sedentary, no HRT (63 \(\pm\) 2 years); 24 sedentary, on HRT (61 \(\pm\) 2 years); 14 AT, not taking HRT (64 \(\pm\) 3 years); and 11 sedentary premenopausal controls (28 \(\pm\) 1 years). CAC, was lower \((P < 0.001)\) in the postmenopausal compared to premenopausal women, regardless of their level of physical activity or use of HRT. However, among the postmenopausal subcategories, CAC was 33-43\% higher in the sedentary HRT and AT groups than in the sedentary, estrogen-deficient peers \((P < 0.05)\).
Furthermore, there were no significant differences between CAC of the sedentary HRT and AT groups, and qualitatively similar findings were observed for β-stiffness and DC between groups. Taken together, these findings suggest that either aerobic exercise training, HRT, or a combination of both can improve arterial stiffening by means of elevated CAC in postmenopausal women.

In the intervention study, the arterial characteristics were evaluated in 12 sedentary postmenopausal women who were using HRT following a 12-week walking-based AT regimen. The home-based exercise intervention consisted of 40 ± 2 minutes per day bouts of walking at 70±1% of their age-determined HRmax. Following the completion of the AT program, CAC and DC increased by ~ 40%, while β-stiffness decreased by ~ 25% (all \( P < 0.05 \)). Furthermore, the absolute values for CAC, DC, and β-stiffness were higher than those observed in the sedentary HRT and AT groups that were obtained from the cross-sectional portion of the study (\( P < 0.05 \)), and were found to improve to levels that mirrored that of the premenopausal women (\( P = 0.24 \)). Taken together, the results suggest that both HRT and habitual aerobic exercise have beneficial effects on CAC, and a short-term aerobically-based exercise intervention can reverse the age-related reduction in CAC in HRT-supplemented postmenopausal women, however, the mechanism(s) responsible for this effect remain equivocal (171).

Sugawara and colleagues (180) investigated the effects of low (40% HRR) and moderate (70% HRR) intensity cycle ergometry-based AT programs (3-5 times per week, 12 weeks at intensities corresponding to 180-300 kcal of energy expenditure) on CAC in postmenopausal women (N=15, 59 ± 6 years). CAC and DC significantly increased post-training in both the low and moderate intensity exercise groups (all, \( P < 0.05 \)), however, these improvements were not significantly different between the exercise intensities if the
energy expenditure between the protocols is similar ($P < 0.05$).

Exercise-induced improvements in CAC can be mediated through modifications in the expression of various vascular structural and functional factors, such as collagen, elastin, ROS, and NO ($^{134;177}$). Long-term AT can reduce and even reverse the progression of age-related arterial stiffness ($^{75;134;164;197}$). AT also mediates improvements in the functional responsiveness of the vasculature and arterial compliance by stimulating elevations in the expression of vasoactive genes and their products ($^{198}$). Furthermore, these aerobically-mediated improvements in CAC occur independent of reductions in traditional CVD risk factors, solidifying the notion that AT reduces overall arterial stiffness ($^{75;164}$).

**Dynamic Strength (Resistance) Training**

The majority of the studies investigating the effects of RT on arterial stiffness indices have thus far dealt with male participants ($^{72-74;199-201}$), leaving a large proportion of the female population without representation. The studies focusing on males have provided the most controversial evidence for the effects of RT on arterial compliance, where some have found improvements ($^{199}$), reductions ($^{72;73;201}$), or no changes in CAC, arterial structural dimensions, or other stiffness indices in both younger ($^{74}$) and older males ($^{200}$).

In contrast, recent evidence has provided consistent support for the potential of RT to improve arterial stiffness in female populations. For example, Fjeldstad et al. ($^{202}$) investigated the effect of lower body RT (2-3 sets of 8 reps at 80% 1RM, 3 times per week for 12 weeks) on small and large arterial compliance in healthy, premenopausal women ($N=32$; RT: $33.2 \pm 2.1$ years, control: $36.8 \pm 3.2$ years). The authors found no
changes in HR, PP, systemic vascular resistance, total vascular impedance or small arterial compliance, while observing a significant time effect for improvements in large artery compliance following the 12-week intervention among the trained and control groups. As these improvements were observed in both groups, the changes cannot be attributed to RT. However, in contrast to previous studies that identified reductions in CAC following RT, no reductions were observed in this female population \(^{(202)}\).

It has been postulated that exercises which incorporate a combination of both AT and RT could provide the appropriate stimulus to facilitate improvements in CAC. This was investigated by Cook \textit{et al.} \(^{(203)}\) who examined and compared the CAC of habitual rowers (a unique exercise that encompasses aerobic and resistance training components) to a sedentary control group (N=30; 50 ± 9 years) matched for age, body mass, metabolic risk factors, sodium intake and BP, finding elevated CAC and reduced $\beta$-stiffness amongst the rowers (rowers; 0.16 ± 0.01 mm$^2$/mmHg versus control; 0.10 ± 0.01 mm$^2$/mmHg, $P < 0.001$). Most recently, Figueroa \textit{et al.} \(^{(204)}\) investigated whether combined long-term RT and AT circuit training can reduce arterial stiffness and MAP in postmenopausal women (N=24; 57.5 ± 11 years). Participants were randomized to a control (n=12) or exercise intervention group (n=12), where the exercisers participated in circuit RT followed by moderate intensity (60% age-determined HR$_{\text{max}}$) AT 3-times per week, for 12-weeks. SBP, DBP, MAP, HR, brachial artery PWV, and dynamic and IHG strength were determined pre- and post-intervention. The exercise intervention produced significant reductions in all of the measured haemodynamic variables (SBP, DBP, MAP, HR), and baPWV (-0.8 ± 0.2 metres/sec), while improving IHG strength (2.8 ± 0.7 vs -0.6 ± 1.2 kg). The authors conclude that the combined RT and AT circuit training program
improves muscular strength, haemodynamics, and arterial stiffness in previously sedentary, postmenopausal women.

Although the findings in males are equivocal, consistent improvements in CAC have been observed in female populations following AT, RT, and a combined aerobic and RT exercise modality. Taken together, these observations suggest that simultaneously performed endurance training may negate the potential stiffening effects of strength training, and the potential exists for beneficial arterial functional responses to RT when it is performed across intensities

**Isometric Training**

The effect of isometric exercise training on arterial compliance has received very little attention in the literature. However, as noted above, AT, RT, and an AT/RT combination have been found to improve CAC and isometric strength in in women, and other female populations with CVD or who are at risk of developing such diseased states.

Although currently equivocal, IHG-mediated reductions in resting BP are thought to occur as a result of neurohumoral, structural, and/or functional modification to TPR following exercise training, where improvements in CAC have been suggested as a centrally-acting mechanism that could augment carotid baroreceptor sensitivity, lower TPR, and ultimately facilitate the IHG-mediated reductions in resting BP.

**1.6 Summary of Background**

As noted in Section 1.1., CVD is the leading cause of death in Canadian women, where elevated arterial BP (HT; ≥120/80 mmHg) greatly increases CVD risk. Although the importance of maintaining a healthy BP is well known, many older women
do not have resting BP values controlled to within target range \(^{(119;120)}\). IHG training is effective in reducing BP in adults, and appears particularly effective in older women. Despite these encouraging findings:

- Most IHG training studies conducted to date are small
- Women have been under-represented within the IHG literature, and

Furthermore, the mechanisms responsible for the IHG-mediated reductions in resting BP remain elusive, yet improved CAC has been suggested as a centrally-acting mechanism that could facilitate the post-training hypotensive response \(^{(132)}\).

Therefore, investigating the effects of IHG training on various indices of cardiovascular health (resting BP and CAC) among postmenopausal women who are at an elevated risk of experiencing HT-related CVD (resting BP \(\geq 120/80\) mmHg) is warranted.

1.7 Thesis Objectives

The primary aim of the proposed study was to examine the effects of IHG training on:

1. Resting BP, and
2. To examine the effects of IHG training on CAC.

1.8 Specific Hypotheses

1. IHG training will lower resting BP, and
2. Increase CAC.
Reference List


(38) De Nucci G, Thomas R, D'Orleans-Juste P, Antunes E, Walder C, Warner TD, Vane JR. Pressor effects of circulating endothelin are limited by its removal in
the pulmonary circulation and by the release of prostacyclin and endothelium-derived relaxing factor. Proc Natl Acad Sci USA 1988; 85:9797-9800.


(68) Photo-electric measurement of blood pressure, volume and flow in the finger. 10th International Conference on Medical and Biological Engineering; 1973.


(141) Lakatta EG. Cardiovascular regulatory mechanisms in advanced age. Physiol Rev 1993; 73:413-467.


(159) Dzau VJ. Significance of the vascular renin-angiotensin pathway. Hypertension 1986; 8:553-559.


(179) Bramwell LC, Hill AV. Velocity transmission of the pulse wave. Lancet 1922; i(891):892.


(199) Kawano H, Tanaka H, Miyachi M. Resistance training and arterial compliance: keeping the benefits while minimizing the stiffening. Hypertension 2006; 24:1753-1759.


Chapter 2: The effects of isometric handgrip training on carotid arterial compliance and resting blood pressure in postmenopausal women

Manuscript
2.1 Introduction

Cardiovascular disease (CVD) is the second most prominent cause of death among Canadians, accounting for ~30% of the national deaths each year \(^1\). The relative risk of developing CVD in Canadian women increases four-fold following the transition into menopause \(^2\), and approximately 80% of all CVD-related mortality is associated with arterial dysfunction and/or disorders \(^3\). Elevations in arterial stiffness (measured by the determination of arterial stiffness indices, such as carotid arterial compliance; CAC) occur with increasing age \(^4,5\), and elevated arterial blood pressure (BP) \(^6,7\). In older women this pathology is particularly concerning, as the process is primarily localized within the large, elastic central arteries (e.g. the carotid) and is correlated with hypertension (HT) and risk of myocardial infarction, heart failure, and cardiovascular-related mortality \(^8\).

The Public Health Agency of Canada considers sustained HT as one of the most important primary risk factors associated with the development of CVD \(^9\). HT afflicts over 7.2 million Canadians \(^9\), where half of those afflicted lie within the 55-74 years of age range. By the 6th decade of life, the decade coinciding with menopause \(^10\), the prevalence of HT in women exceeds that of men \(^9\). Furthermore, recent evidence has identified a positive relationship between resting BP (BP) and CVD-risk occurring with elevations in systolic blood pressure (SBP) by an increment of 20 mmHg or diastolic blood pressure (DBP) by an increment of 10 mmHg within the range of 115/75 mmHg to 185/115 mmHg for individuals between the ages of 40 and 70 years \(^9\). This is particularly concerning for postmenopausal women, as ~39% are pre-HT \(^11\).

Prevention and treatment recommendations for elevated BP include lifestyle
modifications, such as exercise prescription\(^{(12)}\). The weight of the evidence suggests that aerobic and resistance exercises effectively reduce resting BP and improve associated cardiovascular pathologies\(^{(12)}\). More specifically, aerobic training (AT) has been found to reduce resting BP and arterial stiffness in young\(^{(13)}\), elderly\(^{(14)}\), normotensive\(^{(4)}\), and HT individuals\(^{(15)}\). AT has been found to improve CAC in postmenopausal females regardless of hormone-replacement therapy status\(^{(4)}\), where the age-associated reductions in CAC were ~50% less dramatic in AT women than in the age-matched sedentary controls. More recent work has found improvements in arterial stiffness (observed through reductions in brachial artery pulse wave velocity) and isometric forearm muscle strength in postmenopausal women following 12 weeks of combined aerobic and resistance circuit training\(^{(16)}\). Resistance training (RT) can elicit reductions in resting BP by ~3 mmHg,\(^{(17;18)}\) and has also been incorporated within BP management programs. Although the evidence surrounding RT and arterial stiffening in men is controversial, increased CAC has been observed in postmenopausal rowers (a unique exercise that encompasses AT and RT components)\(^{(19)}\), and independently following AT, RT, and a combined AT/RT exercise modality\(^{(20)}\) when compared to sedentary controls. These collective works suggest that the effects of RT preformed at multiple intensities and modalities on CAC and arterial stiffness in postmenopausal women are most beneficial when performed in conjunction with AT\(^{(16;19;20)}\).

Despite the well-known ability of regular exercise to reduce resting BP across populations, women are less likely than men to be consistently physically active and this trend worsens as women age\(^{(21-23)}\). A 2011 Health Report highlighting physical activity trends amongst Canadians reinforces this statistic, reporting that only 14% of women are meeting the currently suggested physical activity recommendations\(^{(22)}\). Furthermore, >
60% of women aged 60 years and above perform little or no sustained physical exercise \((21;24)\), and for those who initially do, adherence to the exercise programs drops by up to ~50% after the initial 6 months of participation \((22;25)\). Therefore, facilitating women’s participation in physical activity at levels that are sufficient to provide the associated health benefits is a significant concern.

Isometric handgrip (IHG) training (4, 2 minute sustained contractions, separated by a timed rest period, performed for a minimum of 3 times per week for up to 10 weeks) is a novel and time-efficient form of exercise training, that has shown, through various small proof-of-concept investigations, to lower resting BP in HT \((26-29)\), and normotensive \((29-31)\) individuals. A recent meta-analysis concluded that IHG-mediated reductions in resting BP appear to occur to a similar, if not greater, degree than those facilitated by AT \((29)\). Additionally, individuals with higher initial resting BP experience greater post-IHG BP reductions \((27)\). To date, women have been underrepresented in the IHG literature, yet available evidence suggests that older women have more pronounced post-IHG training reductions in resting BP than their age-matched, male counterparts \((32)\). Taken together, this work suggests that older women with elevated resting BP may receive the greatest benefit from the IHG intervention. Although the mechanisms associated with the IHG-mediated reductions in resting BP are currently unknown, it has been suggested that improved CAC may play a role \((27)\). To date, no data is available on the effects of IHG training on CAC. With age and/or chronic elevations in Resting BP, the elastic nature of the vasculature is diminished and the central arteries are no longer able to effectively buffer the pulsatile output of the heart \((33)\). The resultant progressive elevation in SBP and reduction in DBP facilitates an increase in arterial pulse pressure (PP), which initiates increases in arterial wall thickness in attempts to normalize arterial wall stress \((34)\). Stiffer
large arteries like the carotid artery are associated with the increased prevalence of isolated systolic HT in postmenopausal women and may partially explain the accelerated rates of established CVD within this population\(^{(35)}\). Improvements in CAC could facilitate the appropriate modifications to total peripheral resistance that would stimulate elevated cardiovagal baroreceptor sensitivity\(^{(19,36)}\), thereby modulating the main neural pathway for acute BP regulation which could effectively reduce resting BP\(^{(37)}\). As mentioned above, women appear to more consistently respond to traditional exercise training with improved CAC, suggesting that it may be a viable mechanism of improved BP regulation with IHG training\(^{(27)}\), as well as a stand-alone cardiovascular benefit of this training modality.

The purpose of this, randomized controlled, parallel-design study (superiority trial)\(^{(38,39)}\) is to investigate the effects of IHG training on CAC in Canadian women who are at an elevated risk for developing HT-related CVD: postmenopausal women with above normal resting BP (SBP \(\geq 120\) and/or DBP >80 mmHg)\(^{(40)}\). The secondary purpose is to replicate the previously observed reductions in resting BP amongst this population. As an exploratory hypothesis, it is expected that the IHG training will improve CAC in a postmenopausal population. It is further hypothesized that reductions in resting BP will be observed following IHG training, thus implicating improved CAC as a mechanism involved with the resting BP attenuation that occurs in response to IHG training among postmenopausal women.

Confirmation of these collective hypotheses will provide the first evidence to support IHG training as a viable method to improve CAC, a prominent HT pathology and independent CVD risk-factor, in women at risk for developing CVD (post-menopausal
women with higher than normal BP), while implicating it as a mechanism of reduced resting BP post-IHG training.

2.2 Methods

Study Participants

Eight non-smoking post-menopausal women (amenorrheic for > 1 year) with higher than normal resting BP (SBP $\geq$ 120 mmHg), were recruited for this two-site study (University of Windsor, Windsor, ON and McMaster University, Hamilton, ON). Exclusion criteria included: a recent medication change (< 1 month), recent hospitalization (< 3 months), hormone replacement therapy, diabetes, autonomic neuropathy, premature ventricular contractions, a paced heart rhythm at rest, heart failure, CVD and those who have any physical limitation which would prevent them from safely and/or effectively performing the IHG exercise.

Study Design

After inquiring about the study, interested individuals were scheduled to meet with study investigators in their city of origin at either i) the Physical Activity and Cardiovascular Research (PACR) lab (Room #240, Kinesiology Building, University of Windsor) or ii) the Vascular Dynamics (VDL) Laboratory (Room #E103 Ivor Wynne Centre, Department of Kinesiology, McMaster University) in order to obtain consent (Appendix K & M) and to determine initial eligibility via a self-administered medical questionnaire (Appendix N). Eligible individuals were then required to obtain their health-care provider support prior to enrollment in the study via a physical activity readiness medical examination questionnaire (Appendix O) and a physician-directed letter of information (Appendix P & Q). After health care provider consent was
obtained, each individual was familiarized to all testing procedures \(^{41}\) and scheduled for baseline testing.

**Testing Protocol**

The testing protocol included 2 series of independent resting BP measurements (performed to initially determine eligibility) followed by a single cardiovascular testing day. To minimize the influence of external factors on the cardiovascular measurements, participants were asked to refrain from the consumption of alcohol or the participation in vigorous exercise for 24 hours prior to each testing session and to avoid caffeine consumption for 12 hours prior \(^{41}\). All testing was conducted at least 4-hours post-prandial, in a quiet, temperature-controlled room (23.5°C ± 1.3°C), and at the same time of day (12:00 ± 2.1 hours). In order to minimize the effects of bladder distension on resting BP measures, all participants were asked to void their bladder prior to each testing session \(^{41,42}\). All participants were tested at baseline (week 0) and upon completion of the IHG training intervention (week 9).

*Testing Day 1 & 2 (approximately 30 minutes per visit, separated by at least 24 hours):* Each participant was assessed after 10-minutes of seated rest, where was measured 4 times (Dinamap Carescape v100, Critikon, Tampa, Florida, USA) in the brachial artery of the left arm, with 2-minutes between each measurement. The last 3 values obtained were averaged on each day to determine their eligibility (BP ≥ 120/80 mmHg for two days, separated by at least 24 hours) \(^{43}\).

*Testing Day 3 (approximately 2 hours):* First, in order to account and control for potential emotional or psychological influences on the measured physiological variables, eligible participants were required to complete the State-Trait anxiety inventory (STAI-S
and STAI-T) in isolation. These two, 20 item questionnaires allow for a tangible, daily and self-reported anxiety score that can represent the potential impact of anxiety on BP regulation. Following the completion of the STAI questionnaire, participants underwent a battery of cardiovascular tests. All of the latter procedures employed were performed in the supine position.

CAC was assessed using standardized testing and analysis procedures. Briefly, resting BP was recorded from the brachial artery after 10-minutes of supine rest using an automated oscillometer (Dinamap Carescape v100, Critikon, Tampa Florida, USA) in order to calibrate the applanation tonometer. Continuous pulse pressure waveforms were subsequently acquired for 1-minute from the right common carotid artery with an applanation tonometer (Millar SPT-301, Millar Instruments, Inc., Houston, Texas, USA), concurrent with the collection of carotid arterial diameters from the left common carotid artery using B-mode ultrasonography (Vivid i, GE Healthcare, Pittsburg, Pennsylvania, USA). A longitudinal image of the cephalic portion of the left common carotid artery was obtained 1-2 cm distal to the carotid bulb and used for analysis. Recordings were obtained for 1-minute, where arterial diameters were measured leading-edge to leading-edge throughout the cardiac cycle using automated edge-detection software and averaged for analysis. CAC was subsequently determined using the following equation:

\[ \text{CAC} = \frac{\pi(D_{\text{max}}/2)^2 - \pi(D_{\text{min}}/2)^2}{\Delta P} \]  

(Equation 1)

where \( \Delta D \) is the change in arterial diameter from systole (\( D_{\text{max}} \)) to diastole (\( D_{\text{min}} \)), and \( \Delta P \) is the tonometrically-obtained arterial PP. All ultrasound images were obtained from the same portions of the carotid artery using anatomic land-marking to ensure accurate comparisons over time. All diameter measurements were made by the same
ultrasonographer using custom-designed, automated-edge detection software (described above) to minimize observer bias. In the current study, the intra-observer reproducibility of CAC assessed was 1% (coefficient of variation) (Appendix C).

To better isolate improved CAC as the potential mechanism mediating reductions in resting BP following IHG training, cardiac output (Q) was assessed using echo/Doppler ultrasonography according to standardized published procedures \(^{(48;52;53)}\). Briefly, following at least 10 minutes of supine rest, the aortic root diameter (ARD) was obtained from the parasternal long-axis view using B-mode ultrasonography with a phased-array probe (3S RS, GE Healthcare, Pittsburg, Pennsylvania, USA) placed to the left of the sternum in the third or fourth intercostal space. Images were measured using electronic calipers that were positioned over the interior edges of the aortic wall echocardiogram. ARD was measured at peak systolic and end diastole over 3 consecutive heart cycles and used for the calculation of ARD using the following equation:

\[
ARD = \frac{1}{3} S_d + \frac{2}{3} D_d
\]

(Equation 2)

where \(S_d\) is the peak systolic arterial diameters and \(D_d\) is the end diastolic arterial diameter. Variance in ARD measures of \(\leq 1\) mm was ensured and is considered acceptable when attempting to assure accurate ARD assessment \(^{(54)}\).

Aortic timed velocity integral (TVI) was then transcutaneously obtained for 1-minute from the ascending aorta using a continuous-wave Doppler transducer (P2D RS, GE Healthcare, Pittsburg, Pennsylvania, USA) placed within the suprasternal notch. The orientation of the probe was manually manipulated in order to obtain the blood velocity profile of the ascending aorta (the highest observed profile concomitant with the perception of rapid onset and cessation of flow and minimal diastolic flow) \(^{(54)}\). The Doppler-derived strove volume (SV; mL) was then calculated according to the following
equation (52):

\[ SV = ARD^2 \cdot (0.785 \cdot TVI) \]  \hspace{1cm} (Equation 3)

and \( Q \) (L/min) was subsequently calculated using the following equation:

\[ Q = \frac{(HR \cdot SV)}{10^3} \]  \hspace{1cm} (Equation 4)

where, HR was the average supine HR recorded during the aortic TVI assessment. To ensure accuracy of the non-invasive determination of \( Q \), the diameter and velocity measures must be obtained from the same location. It can be assumed that the highest systolic aortic velocity will be observed at the level of the narrowest aortic diameter\(^{(54)}\), hence, aortic velocity profiles were obtained after observing the highest aortic blood flow velocity while ARD was measured at the most narrow location within the aortic root. This non-invasive determination of \( Q \) is reproducible and highly correlated with the thermodilution catheterization technique (Ultrasound\( Q = 0.98 \)thermodilution\( Q + 0.17; r=0.96, N=105 \)), allowing for the use of this non-invasive method for the direct determination of \( Q \) without the use of any correction factors\(^{(54)}\).

All signals were sampled at a frequency of 200 Hz, with the exception of the ECG signal (1,000 Hz), and a data acquisition board was used for analogue to digital signal conversion (Powerlab ML 870/P, AD Instruments, Colorado Springs, Colorado, USA) for off-line beat-to-beat analysis, where applicable. All data was acquired and analyzed by the same trained investigator. Measurements were analyzed using LabChart Pro 7 for Windows (AD Instruments, Colorado Springs, Colorado, USA) or automated edge-detection software (Artery Measurement System v2.0, Chalmers University, Göteborg, Sweden), where applicable.
Randomization

Following baseline testing, participants were randomized through stratification by study site (55). The randomization package for each site was identically constructed, where manually generated blocks of 4 and 6 were compiled, ordered and randomly stacked. Next, a unique identifier was labeled on the front of each envelope (eg. 1-W for the 1st participant randomized at the University of Windsor; 1-M for the 1st participant randomized at McMaster University), and subsequently placed in numerical order in a locked filing cabinet until randomization was required. The associated paper was shredded and the empty envelope was stapled to the participants intake file and stored in a locked filing cabinet.

IHG Training Protocol

Following baseline testing, all participants trained 3 times per week, for a total of 8 weeks (26;28;32;43;56). Participants were instructed to record any changes in their exercise, nutritional, and medication status in an exercise log at the onset of every exercise training session. Participants randomized to the IHG-training group completed a bout of IHG exercise: performing 4, 2 minute isometric contractions at 30% of their maximal voluntary contraction (MVC; determined at the onset of each exercise session via electronic linear load cells), using alternate hands with a 1-minute rest period between contractions, on a programmed handgrip dynamometer (ZonaPLUS, Zona HEALTH, Boise, Idaho, USA). Participants who were randomized to the sham-training control group completed a similar bout of IHG exercise, however, at 3% MVC (ZonaPLUS, Zona HEALTH, Boise, Idaho, USA).
Statistical Analysis

Data was analyzed using two-way ANOVA (group x time) for CAC and its associated variables (average carotid diameter, carotid PP), resting BP (SBP, DBP, mean arterial BP; MAP [calculated as 1/3 SBP + 2/3 DBP], and brachial PP; [calculated as SBP – DBP]), and Q (ARD, SV, supine HR), with Tukey’s post hoc procedures used to evaluate specific differences between means, where applicable. Data analysis was completed using IBM SPSS (PASW) Statistics v20 (SPSS Inc., Chicago, IL, USA).

2.3 Results

Participant baseline characteristics are displayed in Table 1. All participant baseline characteristics were similar between the IHG training and the sham-trained control groups (all $P > 0.05$). All participants in the IHG training group completed 24 IHG exercise sessions over the 8-week intervention period. There were no reported long-term changes in exercise, diet, and medication status throughout the investigation in either the IHG training or sham-trained control groups.
Table 1. Participant baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>IHG Training (n = 5)</th>
<th>Sham-trained Control (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67 ± 5</td>
<td>62 ± 7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160 ± 3</td>
<td>162 ± 9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70 ± 18</td>
<td>74 ± 8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27 ± 7</td>
<td>29 ± 6</td>
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<tr>
<td>Resting SBP (mmHg)</td>
<td>138 ± 12</td>
<td>142 ± 22</td>
</tr>
<tr>
<td>Resting DBP (mmHg)</td>
<td>72 ± 5</td>
<td>82 ± 16</td>
</tr>
<tr>
<td>Resting MAP (mmHg)</td>
<td>92 ± 6</td>
<td>101 ± 18</td>
</tr>
<tr>
<td>Resting HR (beats·min⁻¹)</td>
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<td>68 ± 5</td>
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</tr>
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<td>Trait-Anxiety (score/80)</td>
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<td>50 ± 4</td>
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<tr>
<td>B-blocker</td>
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<td>0</td>
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<tr>
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<td>1</td>
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<td>ACE inhibitor + Diuretic</td>
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BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; ACE, angiotensin converting enzyme. Values are mean ± SD.

Effects of Isometric Handgrip Training on Carotid Arterial Compliance, Diameter and Pulse Pressure

IHG training produced no significant changes in CAC, carotid arterial diameters, or pulse pressures (Figure 1). Specifically, CAC remained unchanged within the IHG (0.07 ± 0.01 mm²/mmHg to 0.06 ± 0.02 mm²/mmHg) and sham-trained control (0.06 ± 0.02 mm²/mmHg to 0.07 ± 4.0 x 10⁻³ mm²/mmHg) groups (P = 0.23). Similarly, average carotid arterial diameters (IHG; 6.36 ± 0.62 mm to 6.29 ± 0.74 mm versus sham-trained; 7.12 ± 0.74 mm to 7.01 ± 0.82 mm) and PP (IHG; 46.61 ± 13.98 mmHg to 46.87 ± 17.49 mmHg versus sham-trained; 57.20 ± 3.18 mmHg to 62.57 ± 14.44 mmHg) remained unchanged following the training period (P = 0.75 and P = 0.52, respectively).
Furthermore, reductions in SBP were not correlated with improvements in CAC following the IHG intervention \( [F(1,4) = 0.569, P = 0.317] \).

**Fig 1.**

(a) Effects of 8-weeks of isometric handgrip (IHG) training on (a) CAC, (b) carotid arterial PP, and (c) diameter between the IHG (30% MVC) and sham-training (3% MVC) interventions. Values are means ± SD.
Effects of Isometric Handgrip Training on Resting Blood Pressure

IHG training produced no significant changes in resting systolic BP, diastolic BP, MAP or brachial PP (Figure 2). Specifically, systolic BP remained unchanged within the IHG (138 ± 12 mmHg to 128 ± 18 mmHg) and sham-trained (142 ± 22 mmHg to 138 ± 16 mmHg, \( P = 0.47 \)) groups. Diastolic BP was also unchanged (IHG; 72 ± 5 mmHg to 68 ± 6 mmHg versus Sham-trained; 82 ± 16 mmHg to 75 ± 16 mmHg, \( P = 0.22 \)). Furthermore, IHG training resulted in no significant changes in MAP (IHG; 92 ± 6 mmHg to 88 ± 6 mmHg versus Sham-trained; 102 ± 18 mmHg to 96 ± 16 mmHg, \( P = 0.77 \)) or brachial PP (IHG; 66 ± 7 mmHg to 60 ± 8 mmHg versus Sham; 62 ± 9 mmHg to 63 ± 10 mmHg, \( P = 0.24 \)).
Effects of Isometric Handgrip Training on Anxiety and Cardiac Output

IHG training produced no significant changes in state- and trait- anxiety scores in either the IHG or sham-trained groups (all $P > 0.05$). Furthermore, $Q$ and its associated indices (Table 2) remained unchanged with IHG training (all $P > 0.05$).
Table 2. Measures of cardiac output, pre- to post-intervention

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<tr>
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<td>SV (mL*heart beat⁻¹)</td>
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HR, heart rate; SV, stroke volume; Q, cardiac output. Values are mean ± SD.

2.4 Discussion

Women have been underrepresented in the IHG literature, yet available evidence suggests that older women with elevated resting BP may receive the greatest benefit from this unique form of exercise training. Although the mechanisms associated with the IHG-mediated reductions in resting BP are currently unknown, improved CAC has been proposed as a likely mechanism within this population (27).

The current work is the first prospective, randomized controlled IHG trial to examine the effects of training on arterial compliance while also employing a sham-training intervention as a control group in a population believed to benefit the most from IHG exercise. This work is noteworthy, as investigating the influence of IHG on CAC within this population is essential; in addition to its potential to facilitate BP reductions post-training, its improvement may reduce a women’s overall CVD risk independent of any BP lowering benefit. Second, the use of a sham-training (3% MVC) control group versus a non-exercising control group is important as it attempts to account for a potential placebo effect of the IHG training. Furthermore, as the lowest exercise intensity that can produce significant physiological changes following IHG training has yet to be determined (31), it may serve to inadvertently identify this intensity.

In contrast to the collective hypotheses, 8-weeks of IHG training did not
significantly improve CAC or reduce resting BP, in comparison to a sham-trained control group, within this population of postmenopausal women with above normal BP.

**Effects of Isometric Handgrip Training on Carotid Arterial Compliance**

CAC did not change following the 8-week IHG intervention. In contrast to the findings of the present study, previous work examining the effect of 12-weeks of aerobic training on CAC\(^{(4;49)}\) noted improvements at magnitudes of ~40% among postmenopausal populations (N=12). However, the current observations are in accordance with the works of Fjeldstad *et al.*\(^{(20)}\), who observed no significant changes in CAC in premenopausal women (N=21) following 12-weeks of RT in comparison to a non-exercising control group (N=11). Despite the negative findings, the results of the current study must be interpreted with caution due to the small sample size. The above trials were powered to detect changes in CAC following exercise training, however, the current study did not reach recruitment targets to sufficiently power this work (sample size calculated as n=10 per group for changes in CAC at \(\alpha = 0.05\) and \(\beta = 0.2\))\(^{(28;32)}\).

Furthermore, a longer intervention period may also be required in order to identify significant changes in CAC, as this trial utilized an 8-week intervention while the majority of previous AT and/or RT investigations employed exercise interventions spanning between 10 to 16 weeks\(^{(4;5;15;16;20;47-50;57-59)}\). Adopting a longer training period may produce significant improvements in CAC; however, these improvements may not be associated with resting BP reductions. As many anti-HT medications are known to improve arterial compliance (i.e., ACEIs and diuretics)\(^{(60)}\), it cannot be ruled out that those participants on HT pharmacotherapy may have received maximal CAC benefit prior to enrolling in the study, thus lowering their capacity to respond to the IHG intervention.
with increases in CAC.

The lack of post-training improvements in CAC may also be attributed to the lower stimulus magnitude versus more traditional AT and/or RT stimuli. For instance, during aerobic exercise the continuous, progressive elevation in the pulsatile output of the heart occurs at the appropriate intensity to stimulate modifications to the structural organization of the arterial wall, promoting elevated arterial distensibility, compliance, and reduced stiffness\(^{(60)}\). As HR reaches, on average, maximal values of \(~5\) beats/minute above rest during an IHG training bout\(^{(61-63)}\) concomitant to subtle increases in \(Q\)\(^{(61)}\), it could be speculated that the IHG-mediated elevations in resting HR and/or \(Q\) are not sufficient stimuli to facilitate training-induced structural modifications within the arterial wall. In addition, as MVC did not significantly change in either then IHG or sham-trained groups (all \(P > 0.05\)), this exercise might not provide the required intensities to stimulate arterial re-organizations that would be reflected through improved CAC.

**Effects of Isometric Handgrip Training on Resting Blood Pressure**

Reductions in resting SBP (10 mmHg), MAP (4 mmHg) and brachial PP (5 mmHg) were observed within the intervention group following 8-weeks of IHG training. Although the observed reduction in SBP exceeds the average reported among IHG trainers following an 8-week intervention (-5.7 mmHg)\(^{(27)}\), the current observations were not deemed statistically significant \((P > 0.05)\). However, the IHG-mediated reduction in SBP observed in the present study can be considered *clinically* significant, as reductions between 2-5 mmHg are associated with a reduced risk of stroke (14%), coronary artery disease (9%)\(^{(12)}\) and all-cause mortality (7%)\(^{(64)}\) within the general population. The observations of the current study are similar to those of Stiller-Moldovan *et al.*\(^{(65)}\) who
noted clinically significant reductions in 24-hour, daytime, and nighttime SBP (2 mmHg, 2 mmHg, and 3 mmHg, respectively) following 8-weeks of IHG training in well-controlled medicated HT individuals.

It is important to note that individuals within the sham-trained intervention also experienced reductions in SBP (4 mmHg), DBP (7 mmHg), and MAP (6 mmHg) that can also be considered clinically significant. As this is the first trial to date to investigate the effects of IHG training when performed at 3% MVC, it cannot definitively be determined at this time whether there was a legitimate reduction in resting BP following such a low intensity IHG intervention. Previous work has employed the use of a “sham”-trained control group, however, the individuals simply held the handgrip dynamometer without exhibiting any effort or force \(^{(31)}\). Therefore, attempting to infer responses between the observations obtained within this study from those obtained from Ray and Carrasco \(^{(31)}\) must be done with caution, as the labeling of the groups incites confusion between the actual exercises performed (8 contraction minutes per day of IHG at 3% MVC, performed 3 times per week for 8 weeks, totaling 192 contraction minutes, versus 12 holding minutes of IHG per day at 0% MVC, performed 4 times per week for 5 weeks, totaling 240 holding minutes). Others have also employed similar sham-trained (0.005% MVC) groups within rhythmic isometric training studies, however, further inference cannot be made as post-training BP was not assessed \(^{(66)}\).

The lack of statistically significant changes in resting BP was not only contrary to our hypothesis, but also to the majority of published IHG studies in individuals with above normal BP over a 5- to 8-week training period \(^{(26-28;67;68)}\), including those medicated for HT. However, the data in medicated HT is equivocal, with some noting post-IHG
training reductions in resting BP \(^{(26;27)}\), while others have not \(^{(62;65)}\). Why were there no post-training reductions in resting BP? Unfortunately, as with CAC, the current study was not sufficiently powered to detect statistically significant post-training reductions in resting BP: sample size calculated as \(n=12\) per group for reductions in resting BP at \(\alpha = 0.05\) and \(\beta = 0.2\) \(^{(28;30;31)}\).

However, the use of different HT pharmacotherapies among research cohorts involving individuals medicated for HT may also explain these discrepant findings. ACE inhibitors and diuretic therapy facilitate the downward resetting of the HR arm of the baroreflex when managing BP \(^{(69;70)}\), thus minimizing the potential for IHG-training induced improvements. However, this confounder is likely negligible in the current study, as a smaller proportion of individuals in the 2007 study conducted by McGowan et al. \(^{(26)}\) were receiving ACE inhibitor and/or diuretic therapy than those in the current investigation (64% versus 80% IHG trainers).

The heterogeneous nature of the population in the current study, in that some and not all were receiving medication to treat elevated BP, suggests that greater exposure to the IHG stimulus may be required in order to induce statistically significant post-training reductions in resting BP. Although improvements in resting BP have been observed in medicated and non-medicated HT following training in as little as 8-weeks \(^{(26)}\), the weight of the evidence suggests that individuals medicated for HT may require as much as 10-weeks of IHG training to elicit reductions in resting BP using the traditional 3 times per week, 8-week training protocol \(^{(27;28;65)}\). Taken together, this suggests that in heterogeneous populations whereby some participants are on pharmacotherapy while others are not, greater exposure time to the IHG stimulus may be required. This can be accomplished by either increasing the per-week training frequency within an 8-week
period, or through an extended total training time.

Although statistically nor clinically significant reductions in DBP were not observed within the current study, these observations are in accordance with most \(^{(26,67)}\), but not all \(^{(68)}\) IHG training studies involving individuals with elevated BP (medication and non-medicated).

The evidence provided by this study further supports the effectiveness of IHG training in reducing resting BP (clinical) among individuals who are at an elevated risk for the development of CVD \(^{(65)}\), however, future works with separate populations of postmenopausal women (i.e., medicated and non-medicated), larger sample sizes, and/or longer intervention periods are required to address this question.

**Improved CAC as a Mechanism of BP Reduction following Isometric Handgrip Training**

Improved CAC has been suggested as a potential mechanism involved with the post-IHG training reductions in resting BP \(^{(27)}\). Although there were no statistically significant reductions in resting BP with traditional IHG training at 30\% MVC in the current study, discussion of improved CAC as a mechanism responsible for post-training resting BP attenuation is warranted, as there were clinically relevant reductions in BP with IHG training performed at either 30\% and 3\% MVC. The findings of the current study suggest that improved CAC is not a mechanism of resting BP reduction with IHG training \(F_{(1,4)} = 0.569, P = 0.317\), however, this must be interpreted with caution, as a sufficiently powered investigation of the effects of IHG training on CAC may uphold this hypothesis of benefit. However, the role of exercise intensity, and/or intervention length, and/or medication in the lack of observed changes in CAC cannot be determined. As
such, a large-scale, randomized controlled trial investigating the effects of IHG training intensity and/or intervention length on CAC in medicated and non-medicated postmenopausal women with above normal resting BP is warranted.

To date, the mechanisms associated with the IHG training-induced reductions in resting BP remain elusive. Multiple plausible theories behind the post-IHG training BP attenuations have been proposed in addition to improved CAC-mediated baroreflex function, including: i) improvements in markers of oxidative stress, ii) reductions in tonic sympathetic nerve activity, iii) modifications to autonomic functioning via improved vagal control, iv) ischemia-reperfusion that may mediate improvements in oxidative stress, and/or v) improved endothelial-dependent vasodilatory capacity via increased systemic shear stress. Reductions in total peripheral resistance via one or more of these mechanisms are likely responsible for post-IHG training BP reductions, however, no published literature to date is available on the effect of IHG training on Q, another important index of BP regulation across populations. In the present study, Q and its associated indices (HR and SV) remained unchanged following the 8-week IHG intervention period. This is in accordance with previous work by Spina et al. who investigated the cardiac functional adaptations and their association with improvement cardiovascular fitness (VO2max) in response to a 9-12 month AT program in older, individuals (N=31; 16 females, 64 ± 3 years) with above normal BP (AT: SBP, 129 ± 3 mmHg; DBP, 84 ± 2 mmHg versus Control: SBP, 130 ± 5 mmHg; DBP, 84 ± 5 mmHg). The investigators noted a sex-based difference in the cardiovascular adaptations to training, where training-induced improvements in VO2max were driven by elevations in resting SV in men, while improvements within the female participants were the result of enhanced arterial-venous O2 extraction. These observations are in accordance with
others who have also noted a lack of change in Q following a 26-week RT or AT intervention amongst older men and women (N=57; 72 ± 3 years) with normal or elevated BP \(^{(75)}\). As such, reductions in resting Q are not typically expected in women with above normal BP following exercise training, thereby implicating training-induced reductions in total peripheral resistance as the primary mechanism that is responsible for reductions in resting BP in this population \(^{(8)}\).

### 2.5 Limitations

The results of the current investigation are novel and note-worthy, however, several limitations do exist. The lack of detected significance may certainly lay within the small sample size in the present study (N=8), as sample size calculations based on either: i) elevations in CAC following an AT or RT intervention \(^{(49;59;76)}\), or ii) reductions in mean resting BP post-IHG interventions \(^{(28;30)}\) estimated that 10 and 12 individuals per group, respectively, would be required to detect statistical significance (\(\alpha = 0.05, \beta = 0.2\)). Therefore, results must be considered with caution. Several participants were also being medicated for HT, with a diversity of medication types between individuals. In order to account for the hypotensive effect of medications on arterial function and BP all medications were strictly monitored throughout the study period, and all medications had been maintained for a period of greater than 4-months prior to the study period. This could also be considered a strength of the current investigation, as this is more reflective of individuals with above normal BP in the general population.

### 2.6 Perspectives

Older women stand to achieve the greatest benefit from IHG training, and postmenopausal women with above normal BP are at increased risk of CVD.
development. Reduced CAC occurs as an intrinsic effect of aging and in response to sustained HT; being identified as a prominent CVD risk factor among postmenopausal women \(^{(35)}\) and as a mechanism of BP reductions with IHG training.

This study, conducted in a small sample of postmenopausal women with above normal BP, provides evidence of clinical reductions in BP rest following IHG training, a finding which supports the use of IHG as an efficacious treatment method in the management of elevated BP and may facilitate a reduced risk of CVD-related mortality within this population. However, the primary hypotheses, that 8-weeks of IHG training would produce statistically significant improvements in CAC concomitant with statistically significant reductions in resting BP, were not upheld. Therefore, the use of IHG training to reduce overall CVD risk by means of improvements in CAC can neither be confidently supported nor refuted, nor whether improvements in CAC facilitate reductions in resting BP. Future large-scale, randomized controlled trials designed to investigate the effects of multiple IHG training intensities and/or intervention lengths on CAC and resting BP is required to determine the differing influence of multiple exercise protocols on these variables, and whether training-induced improvements in CAC are associated with reductions in resting BP in multiple populations (i.e., medicated and non-medicated HT).


(44) Spielberger CD. State-trait anxiety inventory. 2010.


(72) Santangelo L, Cigliano L, Montefusco A, Spagnuolo MS, Nigro G, Golino P, Abrescia P. Evaluation of the antioxidant response in the plasma of healthy or


Appendix A: Chapter 1 Figures
Figure 1: Vascular smooth muscle contraction initiated by an action potential travelling along the VSMC membrane. SR, sarcoplasmic reticulum; CMLN, calmodulin; ADP, adenosine diphosphate; ATP, adenosine triphosphate.
Figure 2: The integration of the neural mechanisms responsible for the regulation of arterial blood pressure. ANS: autonomic nervous system, PNS: parasympathetic nervous system, SNS: sympathetic nervous system, HR: heart rate, Receptor, MAP: mean arterial pressure.
Figure 3: Norepinephrine-mediated activation of the α-adrenergic receptor (αAR), and the cellular cascade that results in the NEpi-mediated vasoconstriction. PLC: Phospholipase C, PIP2: phosphatidyl inositol 4,5-bisphosphate; IP3: inositol triphosphate, DAG: diacyl glycerol, SR: sarcoplasmic reticulum, CMLN: calmodulin.
Figure 4: Epinephrine-mediated activation of the β-adrenergic receptor (βAR), and the cellular cascade that results in the E-mediated vasodilation. AC: adenylate cyclase, PKA: protein kinase A, PLN: phospholamban, CMLN: calmodulin.
Figure 6: The renin-angiotensin-aldosterone system (RAAS) and the pathways involved with maintaining arterial blood pressure homeostasis. MAP; mean arterial blood pressure, NE; norepinephrine, ALDO; aldosterone, ADH; anti-diuretic hormone, AR; adrenergic receptor, AT1; angiotensin II type 1 receptor, VSMC; vascular smooth muscle cell, SR; sarcoplasmic reticulum, TPR; total peripheral resistance.
Figure 7: Angiotensin II-mediated vasoconstriction via the activation of the vascular smooth muscle cell membrane angiotensin type I receptor. AT₁; angiotensin type I receptor, PLC; phospholipase C, PIP₂; phosphatidylinositol 4,5-bisphosphate, IP₃; inositol trisphosphate, DAG; diacyl glycerol, SR; sarcoplasmic reticulum, CMLN; calmodulin
Figure 8: ADH (vasopressin)-mediated VSMC contraction initiated by vasopressin type 1 receptor activation. V_{1Rc}; vasopressin type 1 receptor, PLC; phospholipase C, PIP_{2}; phosphatidylinositol 4,5-bisphosphate; IP_{3}; inositol triphosphate, DAG; diacyl glycerol, SR; sarcoplasmic reticum, CMLN; calmodulin, ADP; adenosine diphosphate, ATP; adenosine triphosphate.
Figure 9: The stimulus for the release of atrial natriuretic peptide from the cells of the right atria, and its effects on its innervated organ systems that result in reductions in arterial blood pressure. ANP; atrial natriuretic peptide, RAAS; renin-angiotensin-aldosterone system, ADH; anti-diuretic hormone, AII; angiotensin II, MAP; mean arterial pressure.
Figure 10: A summary of the multiple causes and locations of arterial stiffening. AGE; advanced glycation end-products, MMP; matrix metalloproteinase, TGF-β; transforming growth factor beta, VSMC; vascular smooth muscle cell, NaCl; sodium chloride, SNS; sympathetic nervous system.
Appendix B: Raw Data for Chapter 2
## Participant Characteristics

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*BMI, body mass index; IHG, isometric handgrip; ACEI, angiotensin converting enzyme inhibitor; CCB, calcium channel blocker; BB, beta blocker.*
Pre-training Maximum Voluntary Contraction

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IHG, isometric handgrip

Post-training Maximum Voluntary Contraction

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IHG, isometric handgrip
Pre-training Carotid Arterial Characteristics

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IHG, isometric handgrip; LD\(_{\text{max}}\), maximum lumen diameter; LD\(_{\text{min}}\), minimum lumen diameter; PP, pulse pressure; CAC, carotid arterial compliance.

Post-training Carotid Arterial Characteristics

<table>
<thead>
<tr>
<th>ID</th>
<th>Group</th>
<th>LD(_{\text{max}}) (mm)</th>
<th>LD(_{\text{min}}) (mm)</th>
<th>ARD (mm)</th>
<th>PP (mmHg)</th>
<th>CAC (mm(^2)/mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IHG</td>
<td>6.293</td>
<td>6.006</td>
<td>6.101</td>
<td>43.363</td>
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</tr>
<tr>
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<td>7.129</td>
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<tr>
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<td>6.340</td>
<td>6.473</td>
<td>64.538</td>
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<td>5.956</td>
<td>6.089</td>
<td>57.510</td>
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<td>Sham</td>
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<td>7.535</td>
<td>7.657</td>
<td>51.332</td>
<td>0.0869</td>
</tr>
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IHG, isometric handgrip; LD\(_{\text{max}}\), maximum lumen diameter; LD\(_{\text{min}}\), minimum lumen diameter; PP, pulse pressure; CAC, carotid arterial compliance.
Pre-training Resting Measures

<table>
<thead>
<tr>
<th>ID</th>
<th>Group</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>MAP (mmHg)</th>
<th>HR (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IHG</td>
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<td>72.5</td>
<td>96.6</td>
<td>68.7</td>
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<td>58.2</td>
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<td>81.9</td>
<td>76.2</td>
</tr>
<tr>
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<td>IHG</td>
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<td>75.7</td>
<td>91.2</td>
<td>64.7</td>
</tr>
<tr>
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<td>IHG</td>
<td>133.6</td>
<td>78.0</td>
<td>96.3</td>
<td>63.6</td>
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<td>122.2</td>
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<td>76.4</td>
<td>92.9</td>
<td>74.4</td>
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<tr>
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<td>69.2</td>
<td>90.2</td>
<td>63.9</td>
</tr>
</tbody>
</table>

IHG, isometric handgrip; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; mmHg, millimetres of mercury; bpm, beats per minute

Post-training Resting Measures

<table>
<thead>
<tr>
<th>ID</th>
<th>Group</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
<th>MAP (mmHg)</th>
<th>HR (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IHG</td>
<td>138.9</td>
<td>72.8</td>
<td>94.6</td>
<td>72.3</td>
</tr>
<tr>
<td>2</td>
<td>IHG</td>
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<td>62.1</td>
<td>90.2</td>
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<td>IHG</td>
<td>134.3</td>
<td>63.3</td>
<td>86.8</td>
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<td>IHG</td>
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<td>75.2</td>
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<td>IHG</td>
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<td>66.7</td>
<td>78.5</td>
<td>76.8</td>
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<td>Sham</td>
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<td>92.5</td>
<td>113.4</td>
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<td>62.4</td>
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<td>75.0</td>
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<td>8</td>
<td>Sham</td>
<td>137.6</td>
<td>69.6</td>
<td>92.0</td>
<td>57.5</td>
</tr>
</tbody>
</table>

IHG, isometric handgrip; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; mmHg, millimetres of mercury; bpm, beats per minute
### Pre-testing Echocardiography and Cardiac Output

<table>
<thead>
<tr>
<th>ID</th>
<th>Group</th>
<th>$V_{\text{max}}$ (m/s)</th>
<th>TVI (cm)</th>
<th>$S_d$ (cm)</th>
<th>$D_d$ (cm)</th>
<th>ARD (cm)</th>
<th>SV (mL)</th>
<th>HR (bpm)</th>
<th>$Q$ (L/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IHG</td>
<td>1.173</td>
<td>24.405</td>
<td>2.25</td>
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<td>5.895</td>
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<td>2.080</td>
<td>87.01</td>
<td>52.87</td>
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<td>1.770</td>
<td>56.35</td>
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<td>1.966</td>
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<td>28.137</td>
<td>2.00</td>
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<td>75.08</td>
<td>47.81</td>
<td>3.590</td>
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<td>Sham</td>
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<td>21.474</td>
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<td>2.04</td>
<td>2.152</td>
<td>78.08</td>
<td>57.42</td>
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<td>1.735</td>
<td>52.50</td>
<td>70.45</td>
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<td>Sham</td>
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<td>2.057</td>
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</table>

$V_{\text{max}}$, maximum stroke velocity; TVI, time velocity integral; $S_d$, systolic aortic root diameter; $D_d$, diastolic aortic root diameter; ARD, aortic root diameter; SV, stroke volume; HR, heart rate; $Q$, cardiac output.

### Post-testing Echocardiography and Cardiac Output

<table>
<thead>
<tr>
<th>ID</th>
<th>Group</th>
<th>$V_{\text{max}}$ (m/s)</th>
<th>TVI (cm)</th>
<th>$S_d$ (cm)</th>
<th>$D_d$ (cm)</th>
<th>ARD (cm)</th>
<th>SV (mL)</th>
<th>HR (bpm)</th>
<th>$Q$ (L/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IHG</td>
<td>1.216</td>
<td>25.367</td>
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<td>1.96</td>
<td>2.02</td>
<td>80.94</td>
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<td>1.60</td>
<td>1.71</td>
<td>55.50</td>
<td>60.97</td>
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<td>2.05</td>
<td>69.53</td>
<td>67.33</td>
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<td>1.899</td>
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<td>49.33</td>
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<td>2.139</td>
<td>88.93</td>
<td>60.39</td>
<td>5.370</td>
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<td>Sham</td>
<td>1.292</td>
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<td>1.69</td>
<td>1.764</td>
<td>59.08</td>
<td>72.40</td>
<td>4.277</td>
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<td>1.933</td>
<td>50.11</td>
<td>59.25</td>
<td>2.969</td>
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</table>

$V_{\text{max}}$, maximum stroke velocity; TVI, time velocity integral; $S_d$, systolic aortic root diameter; $D_d$, diastolic aortic root diameter; ARD, aortic root diameter; SV, stroke volume; HR, heart rate; $Q$, cardiac output.
**State-Trait Anxiety Inventory for Adults Form Y-1 (State Anxiety) & Y-2 (Trait Anxiety)**

<table>
<thead>
<tr>
<th>ID</th>
<th>Group</th>
<th>Pre-training</th>
<th>Post-training</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>IHG</td>
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<td>47  46</td>
</tr>
<tr>
<td>2</td>
<td>IHG</td>
<td>47  51</td>
<td>49  55</td>
</tr>
<tr>
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<td>IHG</td>
<td>47  49</td>
<td>48  49</td>
</tr>
<tr>
<td>4</td>
<td>Sham</td>
<td>55  52</td>
<td>62  47</td>
</tr>
<tr>
<td>5</td>
<td>Sham</td>
<td>46  47</td>
<td>41  46</td>
</tr>
</tbody>
</table>

IHG, isometric handgrip; STAI-S, state anxiety; STAI-T, trait anxiety
Appendix C: Statistical Analysis for Chapter 2
Participant Baseline Characteristics

One-Way ANOVA: Baseline Age Between-Group Differences

1a. Age (Means)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>SE</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHG</td>
<td>67.0</td>
<td>2.02</td>
<td>5</td>
</tr>
<tr>
<td>Sham</td>
<td>61.67</td>
<td>3.93</td>
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</table>

1b. Age (All Effects)

ANOVA

<table>
<thead>
<tr>
<th>Age</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>53.333</td>
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<td>53.333</td>
<td>1.832</td>
<td>.225</td>
</tr>
<tr>
<td>Within Groups</td>
<td>174.667</td>
<td>6</td>
<td>29.111</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
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</tbody>
</table>

One-Way ANOVA: Baseline Height Between-Group Differences

2a. Height (Means)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>SE</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHG</td>
<td>160</td>
<td>1.48</td>
<td>5</td>
</tr>
<tr>
<td>Sham</td>
<td>161.67</td>
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2b. Height (All Effects)

ANOVA

<table>
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<tr>
<th>Height</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
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<tbody>
<tr>
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<td>.712</td>
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<tr>
<td>Within Groups</td>
<td>208.667</td>
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<td>34.778</td>
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</tr>
<tr>
<td>Total</td>
<td>213.875</td>
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<td></td>
<td></td>
<td></td>
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</tbody>
</table>
One-Way ANOVA: Baseline Weight Between-Group Differences

3a. Weight (Means)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>SE</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHG</td>
<td>70</td>
<td>8.16</td>
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</tr>
<tr>
<td>Sham</td>
<td>74.3</td>
<td>4.33</td>
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</table>

3b. Weight (All Effects)

ANOVA

<table>
<thead>
<tr>
<th></th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
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</table>

One-way ANOVA: Baseline Body Mass Index Between-Group Differences

4a. BMI (Means)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>SE</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHG</td>
<td>27.3</td>
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</tr>
<tr>
<td>Sham</td>
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</table>

4b. BMI (All Effects)

ANOVA

<table>
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<tr>
<th></th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>4.219</td>
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<td>4.219</td>
<td>.095</td>
<td>.769</td>
</tr>
<tr>
<td>Within Groups</td>
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</tr>
<tr>
<td>Total</td>
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</table>
**One-way ANOVA: Baseline Systolic BP Between-Group Differences**

**5a. Resting Systolic BP (Means)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>SE</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHG</td>
<td>138</td>
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<td>Sham</td>
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**5b. Resting Systolic BP (All Effects)**

ANOVA

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<tr>
<th>SBP_BL</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
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</thead>
<tbody>
<tr>
<td>Between Groups</td>
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<td>.740</td>
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<tr>
<td>Within Groups</td>
<td>1558.828</td>
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<td>259.805</td>
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<td>Total</td>
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</table>

**One-Way ANOVA: Baseline Diastolic BP Between-Group Differences**

**6a. Resting Diastolic BP (Means)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>SE</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHG</td>
<td>72.3</td>
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<tr>
<td>Sham</td>
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**6b. Resting Diastolic BP (All Effects)**

ANOVA

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<tr>
<th>DBP_BL</th>
<th>Sum of Squares</th>
<th>Df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
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</thead>
<tbody>
<tr>
<td>Between Groups</td>
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<td>173.052</td>
<td>1.631</td>
<td>.249</td>
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<tr>
<td>Within Groups</td>
<td>636.691</td>
<td>6</td>
<td>106.115</td>
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</tr>
<tr>
<td>Total</td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
One-way ANOVA: Baseline Mean Arterial BP Between-Group Differences

7a. Resting Mean Arterial BP (Means)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>SE</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHG</td>
<td>91.2</td>
<td>2.70</td>
<td>5</td>
</tr>
<tr>
<td>Sham</td>
<td>101.8</td>
<td>10.24</td>
<td>3</td>
</tr>
</tbody>
</table>

7b. Resting Mean Arterial BP (All Effects)

ANOVA

<table>
<thead>
<tr>
<th>MAP_BL</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>179.707</td>
<td>1</td>
<td>179.707</td>
<td>1.391</td>
<td>.283</td>
</tr>
<tr>
<td>Within Groups</td>
<td>775.312</td>
<td>6</td>
<td>129.219</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>955.019</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

One-way ANOVA: Baseline Brachial Artery PP Between-Group Differences

8a. Resting Brachial PP (Means)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>SE</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHG</td>
<td>65.63</td>
<td>7.55</td>
<td>5</td>
</tr>
<tr>
<td>Sham</td>
<td>60.12</td>
<td>5.16</td>
<td>3</td>
</tr>
</tbody>
</table>

8b. Resting Brachial PP (All Effects)

ANOVA

<table>
<thead>
<tr>
<th>BrachialPP_BL</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>57.029</td>
<td>1</td>
<td>57.029</td>
<td>.263</td>
<td>.626</td>
</tr>
<tr>
<td>Within Groups</td>
<td>1299.434</td>
<td>6</td>
<td>216.572</td>
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<tr>
<td>Total</td>
<td>1356.463</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
One-way ANOVA: Baseline Resting Average Carotid Diameter Between-Group Differences

9a. Resting Average Carotid Diameter (Means)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>SE</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHG</td>
<td>6.36</td>
<td>0.28</td>
<td>5</td>
</tr>
<tr>
<td>Sham</td>
<td>7.12</td>
<td>0.43</td>
<td>3</td>
</tr>
</tbody>
</table>

9b. Resting Average Carotid Diameter (All Effects)

ANOVA

<table>
<thead>
<tr>
<th>CarotidARD_BA</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>1.110</td>
<td>1</td>
<td>1.110</td>
<td>2.506</td>
<td>.164</td>
</tr>
<tr>
<td>Within Groups</td>
<td>2.657</td>
<td>6</td>
<td>.443</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3.768</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

One-way ANOVA: Baseline Resting Carotid Pulse Pressure Between-Group Differences

10a. Resting Carotid Pulse Pressure (Means)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>SE</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHG</td>
<td>46.6</td>
<td>6.25</td>
<td>5</td>
</tr>
<tr>
<td>Sham</td>
<td>57.2</td>
<td>1.83</td>
<td>3</td>
</tr>
</tbody>
</table>

10b. Resting Carotid Pulse Pressure (All Effects)

ANOVA

<table>
<thead>
<tr>
<th>PP_BL</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>210.234</td>
<td>1</td>
<td>210.234</td>
<td>1.573</td>
<td>.256</td>
</tr>
<tr>
<td>Within Groups</td>
<td>802.102</td>
<td>6</td>
<td>133.684</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1012.335</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**One-way ANOVA: Baseline Resting Carotid Arterial Compliance Between-Group Differences**

### 11a. Resting Carotid Arterial Compliance (Means)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>SE</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHG</td>
<td>0.061</td>
<td>0.008</td>
<td>5</td>
</tr>
<tr>
<td>Sham</td>
<td>0.062</td>
<td>0.014</td>
<td>3</td>
</tr>
</tbody>
</table>

### 11b. Resting Carotid Arterial Compliance (All Effects)

**ANOVA**

<table>
<thead>
<tr>
<th>CAC_BL</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>.000</td>
<td>1</td>
<td>.000</td>
<td>.015</td>
<td>.905</td>
</tr>
<tr>
<td>Within Groups</td>
<td>.002</td>
<td>6</td>
<td>.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>.002</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**One-way ANOVA: Baseline Resting Mean Average Aortic Diameter Between-Group Differences**

### 12a. Resting Average Aortic Diameter (Means)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>SE</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHG</td>
<td>1.94</td>
<td>0.06</td>
<td>5</td>
</tr>
<tr>
<td>Sham</td>
<td>1.98</td>
<td>0.13</td>
<td>3</td>
</tr>
</tbody>
</table>

### 12b. Resting Average Aortic Diameter (All Effects)

**ANOVA**

<table>
<thead>
<tr>
<th>AoD_BL</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>.003</td>
<td>1</td>
<td>.003</td>
<td>.091</td>
<td>.773</td>
</tr>
<tr>
<td>Within Groups</td>
<td>.169</td>
<td>6</td>
<td>.028</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>.172</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**One-way ANOVA: Baseline Supine Resting Heart Rate Between-Group Differences**

13a. Supine Resting Heart Rate (Means)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>SE</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHG</td>
<td>61.0</td>
<td>5.07</td>
<td>5</td>
</tr>
<tr>
<td>Sham</td>
<td>63.6</td>
<td>3.77</td>
<td>3</td>
</tr>
</tbody>
</table>

13b. Supine Resting Heart Rate (All Effects)

<table>
<thead>
<tr>
<th>Q_HR_BL</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>13.169</td>
<td>1</td>
<td>13.169</td>
<td>.132</td>
<td>.729</td>
</tr>
<tr>
<td>Within Groups</td>
<td>598.836</td>
<td>6</td>
<td>99.806</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>612.005</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**One-way ANOVA: Baseline Resting Stroke Volume Between-Group Differences**

14a. Resting Stroke Volume (Means)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>SE</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHG</td>
<td>74.997</td>
<td>5.168</td>
<td>5</td>
</tr>
<tr>
<td>Sham</td>
<td>63.55</td>
<td>7.587</td>
<td>3</td>
</tr>
</tbody>
</table>

14b. Resting Stroke Volume (All Effects)

<table>
<thead>
<tr>
<th>StrokeVol_BL</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>245.672</td>
<td>1</td>
<td>245.672</td>
<td>1.676</td>
<td>.243</td>
</tr>
<tr>
<td>Within Groups</td>
<td>879.597</td>
<td>6</td>
<td>146.600</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1125.270</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
One-way ANOVA: Baseline Resting Cardiac Output Between-Group Differences

15a. Resting Cardiac Output (Means)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>SE</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHG</td>
<td>4.52</td>
<td>0.384</td>
<td>5</td>
</tr>
<tr>
<td>Sham</td>
<td>3.99</td>
<td>0.248</td>
<td>3</td>
</tr>
</tbody>
</table>

15b. Resting Cardiac Output (All Effects)

ANOVA

<table>
<thead>
<tr>
<th>Q_BL</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>.537</td>
<td>1</td>
<td>.537</td>
<td>.972</td>
<td>.362</td>
</tr>
<tr>
<td>Within Groups</td>
<td>3.312</td>
<td>6</td>
<td>.552</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3.849</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Effects of IHG Training on Carotid Arterial Pulse Pressure and Compliance

Carotid Arterial Compliance Pre- to Post-IHG Training Repeated Measures ANOVA

1a. Carotid Arterial Compliance (Means)

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Mean</th>
<th>SE</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHG</td>
<td>Pre</td>
<td>0.071</td>
<td>0.008</td>
<td>5</td>
</tr>
<tr>
<td>IHG</td>
<td>Post</td>
<td>0.061</td>
<td>0.007</td>
<td>5</td>
</tr>
<tr>
<td>Sham</td>
<td>Pre</td>
<td>0.062</td>
<td>0.010</td>
<td>3</td>
</tr>
<tr>
<td>Sham</td>
<td>Post</td>
<td>0.072</td>
<td>0.009</td>
<td>3</td>
</tr>
</tbody>
</table>

1b. Carotid Arterial Compliance (All Effects)

<table>
<thead>
<tr>
<th>Effect</th>
<th>SS</th>
<th>Degr. Of Freedom</th>
<th>MS</th>
<th>F</th>
<th>p</th>
<th>Partial eta-squared</th>
<th>Non-centrality</th>
<th>Observed power (α=0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.000</td>
<td>1</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Group</td>
<td>1.14E-005</td>
<td>1</td>
<td>1.14E-005</td>
<td>0.031</td>
<td>0.866</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
</tr>
<tr>
<td>Error</td>
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<td>5</td>
<td>0.000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.000</td>
</tr>
<tr>
<td>TIME</td>
<td>1.79E-008</td>
<td>1</td>
<td>1.79E-008</td>
<td>0.000</td>
<td>0.993</td>
<td>0.000</td>
<td>0.000</td>
<td>0.050</td>
</tr>
<tr>
<td>TIME*Group</td>
<td>0.000</td>
<td>1</td>
<td>0.000</td>
<td>1.794</td>
<td>0.229</td>
<td>0.229</td>
<td>1.794</td>
<td>0.203</td>
</tr>
<tr>
<td>Error</td>
<td>0.001</td>
<td>6</td>
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</tr>
</tbody>
</table>

Carotid Average Arterial Diameter Pre- to Post-IHG Training Repeated Measures ANOVA

2a. Carotid Average Arterial Diameter (Means)

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Mean</th>
<th>SE</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHG</td>
<td>Pre</td>
<td>6.36</td>
<td>0.298</td>
<td>5</td>
</tr>
<tr>
<td>IHG</td>
<td>Post</td>
<td>6.29</td>
<td>0.315</td>
<td>5</td>
</tr>
<tr>
<td>Sham</td>
<td>Pre</td>
<td>7.13</td>
<td>0.384</td>
<td>3</td>
</tr>
<tr>
<td>Sham</td>
<td>Post</td>
<td>7.01</td>
<td>0.407</td>
<td>3</td>
</tr>
</tbody>
</table>

2b. Carotid Average Arterial Diameter (All Effects)

<table>
<thead>
<tr>
<th>Effect</th>
<th>SS</th>
<th>Degr. Of Freedom</th>
<th>MS</th>
<th>F</th>
<th>p</th>
<th>Partial eta-squared</th>
<th>Non-centrality</th>
<th>Observed power (α=0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>672.322</td>
<td>1</td>
<td>672.322</td>
<td>739.892</td>
<td>0.000</td>
<td>0.992</td>
<td>729.892</td>
<td>1.000</td>
</tr>
<tr>
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<td>1</td>
<td>2.093</td>
<td>2.271</td>
<td>0.183</td>
<td>0.273</td>
<td>2.271</td>
<td>0.247</td>
</tr>
<tr>
<td>Error</td>
<td>5.226</td>
<td>6</td>
<td>0.872</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>TIME</td>
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<td>1</td>
<td>0.029</td>
<td>1.662</td>
<td>0.245</td>
<td>0.317</td>
<td>1.662</td>
<td>0.194</td>
</tr>
<tr>
<td>TIME*Group</td>
<td>0.002</td>
<td>1</td>
<td>0.002</td>
<td>0.108</td>
<td>0.754</td>
<td>0.018</td>
<td>0.108</td>
<td>0.059</td>
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<tr>
<td>Error</td>
<td>0.101</td>
<td>6</td>
<td>0.018</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Carotid Arterial Pulse Pressure Pre- to Post-IHG Training Repeated Measures ANOVA

3a. Carotid Arterial Pulse Pressure (Means)

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Mean</th>
<th>SE</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHG</td>
<td>Pre-</td>
<td>46.61</td>
<td>5.171</td>
<td>5</td>
</tr>
<tr>
<td>IHG</td>
<td>Post-</td>
<td>46.87</td>
<td>7.395</td>
<td>5</td>
</tr>
<tr>
<td>Sham</td>
<td>Pre-</td>
<td>57.20</td>
<td>6.675</td>
<td>3</td>
</tr>
<tr>
<td>Sham</td>
<td>Post-</td>
<td>62.57</td>
<td>9.547</td>
<td>3</td>
</tr>
</tbody>
</table>

3b. Carotid Arterial Pulse Pressure (All Effects)

<table>
<thead>
<tr>
<th>Effect</th>
<th>SS</th>
<th>Degr. Of Freedom</th>
<th>MS</th>
<th>F</th>
<th>p</th>
<th>Partial eta-squared</th>
<th>Non-centrality</th>
<th>Observed power (a=0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>22832.201</td>
<td>1</td>
<td>22832.201</td>
<td>119.852</td>
<td>0.000</td>
<td>0.552</td>
<td>119.852</td>
<td>1.000</td>
</tr>
<tr>
<td>Group</td>
<td>547.537</td>
<td>1</td>
<td>547.537</td>
<td>1.821</td>
<td>0.226</td>
<td>0.233</td>
<td>1.821</td>
<td>0.208</td>
</tr>
<tr>
<td>Error</td>
<td>2134.260</td>
<td>6</td>
<td>355.710</td>
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<td></td>
</tr>
<tr>
<td>TIME</td>
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<td>1</td>
<td>29.671</td>
<td>0.977</td>
<td>0.347</td>
<td>0.088</td>
<td>0.577</td>
<td>0.096</td>
</tr>
<tr>
<td>TIME*Group</td>
<td>24.480</td>
<td>6</td>
<td>4.116</td>
<td>0.316</td>
<td>0.074</td>
<td>0.475</td>
<td>0.096</td>
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</tr>
<tr>
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<td>6</td>
<td>51.389</td>
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</table>

4a. Correlation Analysis (CAC and SBP)

<table>
<thead>
<tr>
<th>Group</th>
<th>Variable</th>
<th>CAC</th>
<th>N</th>
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<tr>
<td>IHG</td>
<td>SBP</td>
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<tr>
<td></td>
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<td>p=0.317</td>
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### 5a. Carotid Arterial Diameter Reproducibility

<table>
<thead>
<tr>
<th>ID</th>
<th>Baseline $L_{D_{\text{max}}}$ (mm)</th>
<th>Baseline $L_{D_{\text{min}}}$ (mm)</th>
<th>Reproducibility $L_{D_{\text{max}}}$ (mm)</th>
<th>Reproducibility $L_{D_{\text{min}}}$ (mm)</th>
<th>CV $L_{D_{\text{max}}}$</th>
<th>CV $L_{D_{\text{min}}}$</th>
<th>Difference (day 1-day 2) $L_{D_{\text{max}}}$ (mm)</th>
<th>Difference (day 1-day 2) $L_{D_{\text{min}}}$ (mm)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
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<td>6.356228</td>
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<tr>
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<td>7.087289</td>
<td>7.322622</td>
<td>7.044861</td>
<td>0.012009446</td>
<td>0.004245798</td>
<td>0.125432</td>
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<td>0.042381</td>
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<td>0.130676</td>
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<table>
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<th>Grand Mean</th>
<th>Standard Deviation</th>
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<td>CV</td>
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<td>0.0057</td>
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<tr>
<td>Error Method</td>
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<td>0.08</td>
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</tbody>
</table>

$L_{D_{\text{max}}}$, maximum lumen diameter; $L_{D_{\text{min}}}$, minimum lumen diameter; CV, coefficient of variation
Effects of IHG Training on Resting Blood Pressure and Heart Rate

Resting Systolic BP Pre- to Post-IHG Training Repeated Measures ANOVA

1a. Resting Systolic BP (Means)

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Mean</th>
<th>SE</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHG</td>
<td>Pre-</td>
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<tr>
<td>IHG</td>
<td>Post-</td>
<td>128.39</td>
<td>7.77</td>
<td>5</td>
</tr>
<tr>
<td>Sham</td>
<td>Pre-</td>
<td>142.03</td>
<td>9.31</td>
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</tr>
<tr>
<td>Sham</td>
<td>Post-</td>
<td>138.79</td>
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1b. Resting Systolic BP (All Effects)

<table>
<thead>
<tr>
<th>Effect</th>
<th>SS</th>
<th>Degr. Of Freedom</th>
<th>MS</th>
<th>F</th>
<th>p</th>
<th>Partial eta-squared</th>
<th>Non-centrality</th>
<th>Observed power (α=0.05)</th>
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</thead>
<tbody>
<tr>
<td>Intercept</td>
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<td>0.100</td>
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<tr>
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<td>63.861</td>
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</table>

Resting Diastolic BP Pre- to Post-IHG Training Repeated Measures ANOVA

2a. Resting Diastolic BP (Means)

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
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<th>SE</th>
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<tbody>
<tr>
<td>IHG</td>
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<td>72.30</td>
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<tr>
<td>IHG</td>
<td>Post-</td>
<td>73.19</td>
<td>6.033</td>
<td>5</td>
</tr>
<tr>
<td>Sham</td>
<td>Pre-</td>
<td>81.91</td>
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<tr>
<td>Sham</td>
<td>Post-</td>
<td>74.82</td>
<td>7.789</td>
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2b. Resting Diastolic BP (All Effects)

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<th>Effect</th>
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<th>Degr. Of Freedom</th>
<th>MS</th>
<th>F</th>
<th>p</th>
<th>Partial eta-squared</th>
<th>Non-centrality</th>
<th>Observed power (α=0.05)</th>
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<tbody>
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<td>15628.054</td>
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<td>0.148</td>
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<td>0.239</td>
<td>1.883</td>
<td>0.213</td>
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<tr>
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<td>5.278</td>
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</table>
Resting Mean Arterial BP Pre- to Post-IHG Training Repeated Measures ANOVA

3a. Resting Mean Arterial BP (Means)

<table>
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<tr>
<th>Group</th>
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<th>SE</th>
<th>N</th>
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<tbody>
<tr>
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<td>Sham</td>
<td>Post-</td>
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3b. Resting Mean Arterial BP (All Effects)

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<th>MS</th>
<th>F</th>
<th>p</th>
<th>Partial eta-squared</th>
<th>Non-centrality</th>
<th>Observed power (α=0.05)</th>
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Resting Brachial PP Pre- to Post-IHG Training Repeated Measures ANOVA

4a. Resting Brachial PP (Means)

<table>
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<tr>
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<th>SE</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHG</td>
<td>Pre-</td>
<td>65.63</td>
<td>6.581</td>
<td>5</td>
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<tr>
<td>IHG</td>
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<td>60.37</td>
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<tr>
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</tr>
<tr>
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<td>Post-</td>
<td>63.97</td>
<td>9.655</td>
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4b. Resting Brachial PP (All Effects)

<table>
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<th>MS</th>
<th>F</th>
<th>p</th>
<th>Partial eta-squared</th>
<th>Non-centrality</th>
<th>Observed power (α=0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
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<td>30657.367</td>
<td>129.877</td>
<td>0.000</td>
<td>0.956</td>
<td>129.877</td>
<td>1.000</td>
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<tr>
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<td>0.954</td>
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<td>78.005</td>
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<td>0.245</td>
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<td>1.742</td>
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<td>34.771</td>
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</table>
Effects of IHG Training on Anxiety and Cardiac Output

1a. State Anxiety (IHG Training Group)

State Anxiety Pre- to Post-IHG Training Dependent t-test

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Std. Dev.</th>
<th>N</th>
<th>Diff.</th>
<th>Std. Dev. Diff.</th>
<th>t</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Var1</td>
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<td>4.6188</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Var2</td>
<td>48</td>
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<td></td>
<td>1.6667</td>
<td>5.50757</td>
<td>0.524</td>
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<td>0.652</td>
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</tbody>
</table>

Var1 – IHG STAI-S Pre-
Var2 – IHG STAI-S Post-

1b. Trait Anxiety (IHG Training Group)

Trait Anxiety Pre- to Post-IHG Training Dependent t-test

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Std. Dev.</th>
<th>N</th>
<th>Diff.</th>
<th>Std. Dev. Diff.</th>
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<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Var4</td>
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<td>0.423</td>
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</table>

Var3 – IHG STAI-T Pre-
Var4 – IHG STAI-T Post-
1a. State Anxiety (Sham-trained Group)

*State Anxiety Pre- to Post-IHG Training Dependent t-test*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Std. Dev.</th>
<th>N</th>
<th>Diff.</th>
<th>Std. Dev. Diff.</th>
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<th>df</th>
<th>p</th>
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</thead>
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<td>14.64924</td>
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</tbody>
</table>

Var5 – Sham STAI-S Pre-
Var6 – Sham STAI-S Post-

1b. Trait Anxiety (Sham-trained Group)

*Trait Anxiety Pre- to Post-IHG Training Dependent t-test*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Std. Dev.</th>
<th>N</th>
<th>Diff.</th>
<th>Std. Dev. Diff.</th>
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<th>df</th>
<th>p</th>
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</thead>
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<tr>
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<td>3.000</td>
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</tbody>
</table>

Var6 – Sham STAI-T Pre-
Var7 – Sham STAI-T Post-
Resting Average Aortic Root Diameter Pre- to Post- IHG Training Repeated Measures ANOVA

### 2a. Resting Average Aortic Root Diameter (Means)

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Mean</th>
<th>SE</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHG</td>
<td>Pre-</td>
<td>1.944</td>
<td>0.075</td>
<td>5</td>
</tr>
<tr>
<td>IHG</td>
<td>Post-</td>
<td>1.952</td>
<td>0.074</td>
<td>5</td>
</tr>
<tr>
<td>Sham</td>
<td>Pre-</td>
<td>1.981</td>
<td>0.097</td>
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</tr>
<tr>
<td>Sham</td>
<td>Post-</td>
<td>1.945</td>
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### 2b. Resting Average Aortic Root Diameter (All Effects)

<table>
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<tr>
<th>Effect</th>
<th>SS</th>
<th>Degr. Of Freedom</th>
<th>MS</th>
<th>F</th>
<th>p</th>
<th>Partial eta-squared</th>
<th>Non-centrality</th>
<th>Observed power (n=0.8)</th>
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</thead>
<tbody>
<tr>
<td>Intercept</td>
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<td>1</td>
<td>57.289</td>
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<td>0.000</td>
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<tr>
<td>Group</td>
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<td>0.001</td>
<td>0.016</td>
<td>0.903</td>
<td>0.003</td>
<td>0.016</td>
<td>0.051</td>
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<tr>
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<td>6</td>
<td>0.003</td>
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<td></td>
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<tr>
<td>TIME</td>
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<td>0.001</td>
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<td>0.652</td>
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<td>TIME*Group</td>
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Resting Supine Heart Rate Pre- to Post- IHG Training Repeated Measures ANOVA

### 3a. Resting Supine Heart Rate (Means)

<table>
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<tr>
<th>Group</th>
<th>Time</th>
<th>Mean</th>
<th>SE</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHG</td>
<td>Pre-</td>
<td>60.97</td>
<td>4.468</td>
<td>5</td>
</tr>
<tr>
<td>IHG</td>
<td>Post-</td>
<td>60.64</td>
<td>3.975</td>
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<tr>
<td>Sham</td>
<td>Pre-</td>
<td>63.62</td>
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<tr>
<td>Sham</td>
<td>Post-</td>
<td>64.01</td>
<td>5.132</td>
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### 3b. Resting Supine Heart Rate (All Effects)

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<th>SS</th>
<th>Degr. Of Freedom</th>
<th>MS</th>
<th>F</th>
<th>p</th>
<th>Partial eta-squared</th>
<th>Non-centrality</th>
<th>Observed power (n=0.8)</th>
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</thead>
<tbody>
<tr>
<td>Intercept</td>
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<td>58308.419</td>
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<td>0.660</td>
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<td>957.290</td>
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<td>0.003</td>
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<td>TIME*Group</td>
<td>0.489</td>
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</table>
Resting Stroke Volume Pre- to Post-IHG Training Repeated Measures ANOVA

4a. Resting Stroke Volume (Means)

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<tr>
<th>Group</th>
<th>Time</th>
<th>Mean</th>
<th>SE</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHG</td>
<td>Pre-</td>
<td>75.00</td>
<td>5.415</td>
<td>5</td>
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<tr>
<td>IHG</td>
<td>Post-</td>
<td>80.03</td>
<td>8.922</td>
<td>5</td>
</tr>
<tr>
<td>Sham</td>
<td>Pre-</td>
<td>63.55</td>
<td>6.990</td>
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<tr>
<td>Sham</td>
<td>Post-</td>
<td>66.04</td>
<td>11.518</td>
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4b. Resting Stroke Volume (All Effects)

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<th>Effect</th>
<th>SS</th>
<th>Degr. Of Freedom</th>
<th>MS</th>
<th>F</th>
<th>p</th>
<th>Partial eta-squared</th>
<th>Non-centrality</th>
<th>Observed power (α=0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>75842.499</td>
<td>1</td>
<td>75842.499</td>
<td>156.823</td>
<td>0.000</td>
<td>0.863</td>
<td>156.823</td>
<td>1.000</td>
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<tr>
<td>Group</td>
<td>605.774</td>
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<td>605.774</td>
<td>1.223</td>
<td>0.368</td>
<td>0.173</td>
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<td>Error</td>
<td>484.236</td>
<td>8</td>
<td>60.530</td>
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<td>0.500</td>
<td>0.123</td>
<td>0.879</td>
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<td>TIME*Group</td>
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<td>Error</td>
<td>301.881</td>
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<td>60.376</td>
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</table>

Resting Cardiac Output Pre- to Post-IHG Training Repeated Measures ANOVA

5a. Resting Cardiac Output (Means)

<table>
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<tr>
<th>Group</th>
<th>Time</th>
<th>Mean</th>
<th>SE</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHG</td>
<td>Pre-</td>
<td>4.52</td>
<td>0.332</td>
<td>5</td>
</tr>
<tr>
<td>IHG</td>
<td>Post-</td>
<td>4.78</td>
<td>0.494</td>
<td>5</td>
</tr>
<tr>
<td>Sham</td>
<td>Pre-</td>
<td>3.99</td>
<td>0.429</td>
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</tr>
<tr>
<td>Sham</td>
<td>Post-</td>
<td>4.21</td>
<td>0.638</td>
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</table>

5b. Resting Cardiac Output (All Effects)

<table>
<thead>
<tr>
<th>Effect</th>
<th>SS</th>
<th>Degr. Of Freedom</th>
<th>MS</th>
<th>F</th>
<th>p</th>
<th>Partial eta-squared</th>
<th>Non-centrality</th>
<th>Observed power (α=0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>287.152</td>
<td>1</td>
<td>287.152</td>
<td>192.794</td>
<td>0.000</td>
<td>0.970</td>
<td>192.794</td>
<td>1.000</td>
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<tr>
<td>Group</td>
<td>1.165</td>
<td>1</td>
<td>1.165</td>
<td>0.189</td>
<td>0.668</td>
<td>0.017</td>
<td>0.193</td>
<td>0.138</td>
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<td>Error</td>
<td>5.800</td>
<td>6</td>
<td>1.457</td>
<td>4.353</td>
<td>0.002</td>
<td>0.104</td>
<td>0.069</td>
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<tr>
<td>TIME</td>
<td>0.313</td>
<td>1</td>
<td>0.313</td>
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<td>0.002</td>
<td>1</td>
<td>0.002</td>
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<td>0.030</td>
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<td>1.852</td>
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<td>4.353</td>
<td>0.002</td>
<td>0.104</td>
<td>0.069</td>
<td>0.160</td>
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</table>
Effects of IHG training on Maximum Voluntary Contraction

Maximum Voluntary Contraction Pre- to Post-IHG Training Repeated Measures ANOVA

1a. Maximum Voluntary Contraction (Means)

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>Mean</th>
<th>SE</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHG</td>
<td>Pre-</td>
<td>58.0</td>
<td>2.817</td>
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<td>IHG</td>
<td>Post-</td>
<td>65.8</td>
<td>3.636</td>
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<td>Sham</td>
<td>Pre-</td>
<td>51.0</td>
<td>5.699</td>
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<td>Sham</td>
<td>Post-</td>
<td>59.7</td>
<td>7.357</td>
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1b. Maximum Voluntary Contraction (All Effects)

<table>
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<th>Effect</th>
<th>SS</th>
<th>Deg. Of Freedom</th>
<th>MS</th>
<th>F</th>
<th>p</th>
<th>Partial eta-squared</th>
<th>Non-centrality</th>
<th>Observed power (α=0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
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<td>47166.084</td>
<td>445.770</td>
<td>0.000</td>
<td>0.897</td>
<td>442.770</td>
<td>1.000</td>
</tr>
<tr>
<td>Group</td>
<td>308.959</td>
<td>1</td>
<td>308.959</td>
<td>4.778</td>
<td>0.031</td>
<td>0.142</td>
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</tr>
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<td>530.150</td>
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<td>106.025</td>
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<td>95.525</td>
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</table>
Appendix D: University of Windsor Research Ethics Board Clearance
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 clearance 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 clearance 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 participants and/or affecting significantly the conduct of the study;

b) all adverse and unexpected experiences in 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 plan 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.

Sincerely,

[Signature]

[Name]

Chair, Research Ethics Board

cc: [Name], Research Ethics Coordinator

This is an official document. Please retain the original in your files.
Appendix E: McMaster University Research Ethics Board Clearance
M.H.K. Thesis – M. Gregory

Windsor – Applied Human Performance

RESEARCH ETHICS BOARD

REB Office, 293 Wellington St. N., Suite 102, Hamilton, ON L8L 8E7
Telephone: 905-521-3100, Ext. 42013
Fax: 905-577-8379

April 11, 2012

PROJECT NUMBER: 12-113

PROJECT TITLE: Isometric handgrip training and arterial blood pressure in post-menopausal women

PRINCIPAL INVESTIGATOR: Michael Gregory
LOCAL PI: Dr. Maureen MacDonald

This will acknowledge receipt of your e-mail and letter dated April 3, 2012 which enclosed a copy of the revised Letter of Information/Consent, the revised study protocol along with a very detailed response to the specific issues raised by the Research Ethics Board at their meeting held on February 21, 2012. Based on this additional information, we wish to advise your study has been given final approval from the full REB. The Study Protocol, including the Letter of Information/Consent version 4 dated April 10, 2012 along with the Appendix R (Advertisement); Appendix B (Questionnaire), Appendix C (Par-medX form); Appendix D (Health Care Provider Documents; Appendix P (Participant Recruitment Poster); Appendix Q (Participant Recruitment Handout) and Appendix O (Daily Exercise Log Sheet) all versions dated 11/14/2011 were found to be acceptable on both ethical and scientific grounds. Please note attached you will find the Information/Consent Form and the recruitment poster with the REB approval affixed; all consent forms and posters/flyers used in this study must be copies of the attached materials.

We are pleased to issue final approval for the above-named study for a period of 12 months from the date of the REB meeting on February 21, 2012. Continuation beyond that date will require further review and renewal of REB approval. Any changes or revisions to the original submission must be submitted on an REB amendment form for review and approval by the Research Ethics Board.

The Hamilton Health Sciences/McMaster Health Sciences Research Ethics Board operates in compliance with and is constituted in accordance with the requirements of: The Tri-Council Policy Statement on Ethical Conduct of Research Involving Humans; The International Conference on Harmonization of Good Clinical Practices; Part C Division 5 of the Food and Drug Regulations of Health Canada; and the provisions of the Ontario Personal Health Information Protection Act 2004 and its applicable Regulations.

PLEASE QUOTE THE ABOVE-REFERENCE PROJECT NUMBER ON ALL FUTURE CORRESPONDENCE

Sincerely,

S. Salama
Suzette Salama PhD.
Chair, Research Ethics Board
Appendix F: University of Windsor Poster Advertisement
Are you a female resident of Windsor who is post-menopausal?

Have you been diagnosed with high blood pressure?

If you answered yes to the previous questions, you may be eligible to participate in a Research Study. Dr. Cheri McGowan and graduate student Mike Gregory 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 isometric handgrip exercise on blood pressure.

<table>
<thead>
<tr>
<th>If you are interested or would like to know more information, please contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. McGowan</td>
</tr>
<tr>
<td>Mike Gregory</td>
</tr>
</tbody>
</table>

<p>| 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |</p>
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</tr>
</tbody>
</table>
Appendix G: McMaster University Poster Advertisement
Post-menopausal women are invited to participate in a Research Study

Are you, your friend, or a family member a female resident of the Hamilton area who is post-menopausal?

Have you been diagnosed with high blood pressure?

If you answered yes to the previous questions, you may be eligible to participate in a Research Study taking place at McMaster University, examining the effects of isometric handgrip exercise on blood pressure.

| If you are interested or would like to know more information, please contact |
|-----------------------------|-----------------------------|-----------------------------|
| Dr. MacDonald               | (905)-525-9140 ext. 23580  | macdonml@mcmaster.ca        |
| Mike Gregory                | (519)-253-3000 ext. 2451  | gregorym@uwindsor.ca        |

Ver. 1. January 16th, 2012
Appendix H: University of Windsor Website Advertisement
Attention all postmenopausal women:

We are looking for participants to take part in a research study at the University of Windsor, conducted by Drs. Cheri McGowan and Kevin Milne. We are investigating the effects of isometric handgrip exercise on blood pressure. For more information please contact Dr. Cheri McGowan at 519-253-3000 ext. 2451 & 4979, or mcgowanc@uwindsor.ca, and/or study investigator Mike Gregory at 519-253-3000 ext. 2451 or gregorym@uwindsor.ca. This study has been cleared by the University of Windsor research Ethics Board.
Appendix I: Windsor Star Newspaper Advertisement

Attention all postmenopausal women:
We are looking for participants to take part in a research study at the University of Windsor, conducted by Drs. Cheri McGowan and Kevin Milne. We are investigating the effects of isometric handgrip exercise on blood pressure. For more information please contact Dr. Cheri McGowan at 519-253-3000 ext. 2451 & 4979, or mcgowanc@uwindsor.ca, and/or study investigator Mike Gregory at 519-253-3000 ext. 2451 or gregorym@uwindsor.ca. This study has been cleared by the University of Windsor research Ethics Board.
Attention all postmenopausal women:

Appendix J: Hamilton Spectator Newspaper Advertisement
You may be eligible to participate in a research study at McMaster University, being conducted by Dr. Maureen MacDonald and graduate student Mike Gregory. We are investigating the effects of isometric handgrip exercise on blood pressure. For more information please contact Dr. Maureen MacDonald at 905-525-9140 ext. 27037.
Appendix K: University of Windsor Consent to Participate in Research Form
Title of Study: Isometric handgrip training and arterial blood pressure in post-menopausal women

(University of Windsor site; PROTOCOL 1)

You are asked to participate in a research study conducted by Drs. Cheri McGowan and Kevin Milne, from the Department of Kinesiology at the University of Windsor.

If you have any questions or concerns about the research, please feel to contact Dr. Cheri McGowan via telephone (519-253-3000 ext. 2451 or 4979) or email (mcgowanc@uwindsor.ca) or Dr. Kevin Milne (Telephone: 519-253-3000 ex. 2452; Email: kjmilne@uwindsor.ca). For questions or concerns during non-working hours, please contact Dr. Cheri McGowan via cell phone at 734-904-8488.

PURPOSE OF THE STUDY

After menopause, women are at high risk of developing high blood pressure and cardiovascular disease. This study tests the theory that in post-menopausal women with and without high blood pressure, a simple form of exercise training, isometric handgrip training, will lower blood pressure at rest, and during activities of daily life. Our study also tests the theory that this type of training will improve the ability of the heart to vary its rhythm and quiet the nervous system. In addition, we expect that certain regulatory substances in the blood (e.g. adrenaline) will be reduced, as will the tension in the arteries of your neck, and the efficiency of your heart will be improved.

PROCEDURES

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

Inclusion Criteria/Informed Consent/Familiarization Procedures

Visit 1 (30 minutes):

After expressing interest in the study, if you meet the study’s qualifications, you will be invited to meet the investigators at the Physical Activity and Cardiovascular Research Laboratory (PACR; Room #240, Human Kinetics Building, University of Windsor). At that time, you will be asked to read the consent form and information sheet on the study. After meeting with the study investigators, you will be shown 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 sign the informed consent, you will fill out a short medical questionnaire, and a physical activity (PARmed-X) questionnaire which you will take to your health care provider for him or her to complete. We encourage you to ask any questions related to the study at this time.

Visit 2 (1 hour):

After agreeing to participate in the study, and if you are eligible, you will undergo a practice test visit. With the exception of the blood draw, we will let you practice all portions of the investigation (e.g., measurement of blood pressure and heart rate).
Measurement Procedures- 3rd visit to completion of investigation:

You will undergo the first testing session in the PACR Lab (Room #240, Human Kinetics Building, University of Windsor). To minimize outside factors on our measures, you will be asked to not have alcohol and to not exercise vigorously for 24-hours before each testing session. You will also be asked to avoid caffeine for 12-hours before the tests. All testing will take place at the same time of day, in a quiet, temperature-controlled room. On testing days, you will be asked to empty your bladder, as a full bladder can increase blood pressure.

Testing Days 1 and 2 (approximately 0.5 hours): Your resting blood pressure will be measured in your upper arm after 10 minutes of seated rest. Your blood pressure will be measured 4 times, with 2-minutes of rest between measures. This will be repeated again at least 24-hours after Testing Day 1.

If you are still eligible to be in the study, the following testing days will occur:

Testing Day 3 (approximately 45 minutes): Twelve hours after your last meal, and after lying down for 30 minutes, your blood will be taken. Five mL of blood will be collected from a vein in your arm by a registered practicing nurse. We will use this blood sample to measure blood values of nervous system activity ("fight or flight" system), oxidative stress (chemical reaction which can have a negative effect on many cells of the body including the heart and blood vessels), blood sugar and cholesterol.

Testing Day 4 (approximately 2 hours): Upon arrival at the PACR lab and at least 4 hours following your last meal, you will complete a self-administered questionnaire (State-Trait anxiety inventory) in an attempt to control for any possible variability in the cardiovascular testing measurements performed during this testing session which could occur as a result of your current emotional state. After which, your resting blood pressure will be measured after 10 minutes of seated rest, in the same way that it was measured during Testing Days 1 and 2. Your heart rate will be monitored as well, using 3 sticker-electrodes that will be placed on your chest. Your breathing frequency will be measured using a breathing belt placed around your chest.

A technique called microneurography will then be used to measure, just below your knee, impulses travelling in a nerve to your calf muscle. This procedure has 2 parts. First, the position of your nerve will be mapped out using a pen-shaped instrument that emits a small electrical pulse. This will cause the muscles in your lower leg to twitch or tingle. This will be a strange sensation but will not be painful, and the sensations will disappear when the stimulation stops. A tiny, sterile wire electrode (about the size of a large human hair) will then be inserted through your skin and positioned just under the skin about 2-3 centimetres from the nerve site. This will be followed by the placement of a second tiny electrode, through your skin, into the nerve. The second electrode will be moved around, until the appropriate recording site is found. The electrode will remain in the nerve throughout the experiment. In most people, a satisfactory recording may be obtained after 20-30 minutes, but in some people, a good site cannot be found, or nerve activity is so low we cannot tell whether the best site has been found. If a good site cannot be located within 45 minutes, the procedure will stop. Once a proper recording site is
obtained, your heart rate, blood pressure, breathing rate and nerve impulses will be recorded continuously for about 10 minutes.

Next, we will measure the pressure of blood flowing through the carotid artery located in your neck, as well as the diameter of the vessel. While still lying down, a pencil-like probe will be placed gently against your carotid artery on the right side of your neck and held lightly for a total of 2 minutes. On the opposite side, an image of the diameter of this same artery will be taken using an ultrasound wand. We will then use ultrasound to measure the amount of blood pumped from your heart, by holding a smaller ultrasound wand over your heart and in the notch above your breast bone.

At the end of the testing session, we will send you home with a device that will record your blood pressure for the next 24-hours. The morning following, you will return this device to the Department of Kinesiology’s front office (General Office, Department of Kinesiology, Faculty of Human Kinetics, University of Windsor).

Following baseline testing, you will be assigned, at random (by chance), to an isometric handgrip training group or a sham training group. If you are randomized to the isometric handgrip training group, you will train 3 times per week, for a total of 8-weeks. You will perform 4, 2-minute squeezes at 30% of your maximum squeeze, using both hands (each separated by 1 minute of rest) on a computerized handgrip. If you are randomized to the sham training group, you will perform 4, 2-minute squeezes at 3% (instead of 30%) of your maximum squeeze. All training sessions per week will take place under the supervision of an exercise trainer, where your resting blood pressure will be measured before each session. Training sessions should not last longer than 30 minutes. Your exercise, nutritional, and medication status (where necessary) will be monitored throughout the study to make sure they do not change. Your health care provider will also be informed of the importance of keeping exercise, nutrition and medication status unchanged throughout the investigation, with the request of notifying one of the study investigators if one or more of these variables change. At the end of the 8-weeks, all baseline tests will be repeated.

**POTENTIAL RISKS AND DISCOMFORTS**

You may experience tendonitis in the tendons of the training arms with handgrip training however this risk is minimal if the exercise is properly performed. The blood pressure and blood flow measurement procedures are non-invasive but you may experience numbness and/or tingling in the limb with the cuff(s) while we are taking our measurements. The gel used to image your heart and/or the sticker-electrodes used to measure your heart rate may cause a skin irritation however, this risk is minimal.

The insertion of a needle for blood sampling is common practice and involves few risks. There is local yet transient discomfort with the insertion of the needle, and there is a theoretical risk of infection, however blood draws will be made under completely sterile conditions. After we take out this needle, we will press firmly on the skin to minimize bruising.

Microneurography has been shown to be a safe method for measuring sympathetic nerve traffic to muscle. Microneurography has been used in laboratories all over the world with only 3
complications in the last 40 years, the worst of which was a slight weakness of the muscle of the leg lasting 2 to 6 months. You may notice a mild ache in the muscles of the right leg for a few days after the procedure.

Please contact one of the study investigators if you feel any adverse effects from completing any portion of the study, and/or if you have any questions or concerns. Exercise leaders and study investigators will reinforce proper training technique throughout the study intervention period. If you experience any adverse effects during any testing procedure, first line response will be provided.

POTENTIAL BENEFITS TO SUBJECTS AND/OR TO SOCIETY

You may or may NOT experience a lower blood pressure at rest or during your activities of daily life after each part of the study. In addition, you may or may not have improvements in the ability of your heart to vary its rhythm, a decrease in the activity of your nervous system, reduced tension in the blood vessels of your neck, an increase in the efficiency of the work of your heart, and/or reduced oxidative stress.

If we prove our theories, isometric handgrip training may be a possible prevention and/or treatment option for post-menopausal women, like you.

PAYMENT FOR PARTICIPATION

You will receive a Human Kinetics T-shirt for your participation, and will be reimbursed for parking costs over the course of the 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 your confidentiality, following your consent, you will be assigned an identification number. Your name will not be mentioned in any publication or presentation, and you will be identified with only your identification number on all collection tools (electronic or otherwise). All paper data and all electronic data will be stored in the locked laboratory (PACR Lab, Room #240, Human Kinetics Building, University of Windsor) of the study investigators. Information stored on computer will be password-accessible only. With respect to final disposal, all paper records (including medical and physical activity readiness 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 wish to answer and still remain in the study. The investigator may withdraw you from this research if circumstances arise which warrant doing so (e.g., medication, nutrition and/or physical activity change).
FEEDBACK OF THE RESULTS OF THIS STUDY TO THE SUBJECTS

You 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 (http://www.uwindsor.ca/reb) at the completion of the study.

SUBSEQUENT USE OF DATA

This data may be used in subsequent studies however your privacy will be upheld with the use of your unique subject identification number under all circumstances.

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 Isometric handgrip training and arterial blood pressure in post-menopausal women – effects and mechanisms (University of Windsor site; PROTOCOL 1) 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 April 2009
Appendix L: University of Windsor Letter of Information for Consent to Participate in Research Form
LETTER OF INFORMATION FOR CONSENT TO PARTICIPATE IN RESEARCH

Title of Study: Isometric handgrip training and arterial blood pressure in post-menopausal women

(University of Windsor site; PROTOCOL 1)

You are asked to participate in a research study conducted by Drs. Cheri McGowan and Kevin Milne, from the Department of Kinesiology at the University of Windsor.

If you have any questions or concerns about the research, please feel to contact Dr. Cheri McGowan via telephone (519-253-3000 ext. 2451 or 4979) or email (mcgowanc@uwindsor.ca) or Dr. Kevin Milne (Telephone: 519-253-3000 ex. 2452; Email: kjmilne@uwindsor.ca). For questions or concerns during non-working hours, please contact Dr. Cheri McGowan via cell phone at 734-904-8488.

PURPOSE OF THE STUDY

After menopause, women are at high risk of developing high blood pressure and cardiovascular disease. This study tests the theory that in post-menopausal women with and without high blood pressure, a simple form of exercise training, isometric handgrip training, will lower blood pressure at rest, and during activities of daily life. Our study also tests the theory that this type of training will improve the ability of the heart to vary its rhythm and quiet the nervous system. In addition, we expect that certain regulatory substances in the blood (e.g. adrenaline) will be reduced, as will the tension in the arteries of your neck, and the efficiency of your heart will be improved.

PROCEDURES

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

Inclusion Criteria/Informed Consent/Familiarization Procedures

Visit 1 (30 minutes):

After expressing interest in the study, if you meet the study’s qualifications, you will be invited to meet the investigators at the Physical Activity and Cardiovascular Research Laboratory (PACR; Room #240, Human Kinetics Building, University of Windsor). At that time, you will be asked to read the consent form and information sheet on the study. After meeting with the study investigators, you will be shown 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 sign the informed consent, you will fill out a short medical questionnaire, and a physical activity (PARmed-X) questionnaire which you will take to your health care provider for him or her to complete. We encourage you to ask any questions related to the study at this time.

Visit 2 (1 hour):
M.H.K. Thesis – M. Gregory

After agreeing to participate in the study, and if you are eligible, you will undergo a practice test visit. With the exception of the blood draw, we will let you practice all portions of the investigation (e.g., measurement of blood pressure and heart rate).

Measurement Procedures- 3rd visit to completion of investigation:

You will undergo the first testing session in the PACR Lab (Room #240, Human Kinetics Building, University of Windsor). To minimize outside factors on our measures, you will be asked to not have alcohol and to not exercise vigorously for 24-hours before each testing session. You will also be asked to avoid caffeine for 12-hours before the tests. All testing will take place at the same time of day, in a quiet, temperature-controlled room. On testing days, you will be asked to empty your bladder, as a full bladder can increase blood pressure.

Testing Days 1 and 2 (approximately 0.5 hours): Your resting blood pressure will be measured in your upper arm after 10 minutes of seated rest. Your blood pressure will be measured 4 times, with 2-minutes of rest between measures. This will be repeated again at least 24-hours after Testing Day 1.

If you are still eligible to be in the study, the following testing days will occur:

Testing Day 3 (approximately 45 minutes): Twelve hours after your last meal, and after lying down for 30 minutes, your blood will be taken. Five mL of blood will be collected from a vein in your arm by a registered practicing nurse. We will use this blood sample to measure blood values of nervous system activity (“fight or flight” system), oxidative stress (chemical reaction which can have a negative effect on many cells of the body including the heart and blood vessels), blood sugar and cholesterol.

Testing Day 4 (approximately 2 hours): Upon arrival at the PACR lab and at least 4 hours following your last meal, you will complete a self-administered questionnaire (State-Trait anxiety inventory) in an attempt to control for any possible variability in the cardiovascular testing measurements performed during this testing session which could occur as a result of your current emotional state. After which, your resting blood pressure will be measured after 10 minutes of seated rest, in the same way that it was measured during Testing Days 1 and 2. Your heart rate will be monitored as well, using 3 sticker-electrodes that will be placed on your chest. Your breathing frequency will be measured using a breathing belt placed around your chest.

A technique called microneurography will then be used to measure, just below your knee, impulses travelling in a nerve to your calf muscle. This procedure has 2 parts. First, the position of your nerve will be mapped out using a pen-shaped instrument that emits a small electrical pulse. This will cause the muscles in your lower leg to twitch or tingle. This will be a strange sensation but will not be painful, and the sensations will disappear when the stimulation stops. A tiny, sterile wire electrode (about the size of a large human hair) will then be inserted through your skin and positioned just under the skin about 2-3 centimetres from the nerve site. This will be followed by the placement of a second tiny electrode, through your skin, into the nerve. The second electrode will be moved around, until the appropriate recording site is found. The electrode will remain in the nerve throughout the experiment. In most people, a satisfactory recording may be obtained after 20-30 minutes, but in some people, a good site cannot be found,
or nerve activity is so low we cannot tell whether the best site has been found. If a good site cannot be located within 45 minutes, the procedure will stop. Once a proper recording site is obtained, your heart rate, blood pressure, breathing rate and nerve impulses will be recorded continuously for about 10 minutes.

Next, we will measure the pressure of blood flowing through the carotid artery located in your neck, as well as the diameter of the vessel. While still lying down, a pencil-like probe will be placed gently against your carotid artery on the right side of your neck and held lightly for a total of 2 minutes. On the opposite side, an image of the diameter of this same artery will be taken using an ultrasound wand. We will then use ultrasound to measure the amount of blood pumped from your heart, by holding a smaller ultrasound wand over your heart and in the notch above your breast bone.

At the end of the testing session, we will send you home with a device that will record your blood pressure for the next 24-hours. The morning following, you will return this device to the Department of Kinesiology’s front office (General Office, Department of Kinesiology, Faculty of Human Kinetics, University of Windsor).

Following baseline testing, you will be assigned, at random (by chance), to an isometric handgrip training group or a sham training group. If you are randomized to the isometric handgrip training group, you will train 3 times per week, for a total of 8-weeks. You will perform 4, 2-minute squeezes at 30% of your maximum squeeze, using both hands (each separated by 1 minute of rest) on a computerized handgrip. If you are randomized to the sham training group, you will perform 4, 2-minute squeezes at 3% (instead of 30%) of your maximum squeeze. All training sessions per week will take place under the supervision of an exercise trainer, where your resting blood pressure will be measured before each session. Training sessions should not last longer than 30 minutes. Your exercise, nutritional, and medication status (where necessary) will be monitored throughout the study to make sure they do not change. Your health care provider will also be informed of the importance of keeping exercise, nutrition and medication status unchanged throughout the investigation, with the request of notifying one of the study investigators if one or more of these variables change. At the end of the 8-weeks, all baseline tests will be repeated.

POTENTIAL RISKS AND DISCOMFORTS

You may experience tendonitis in the tendons of the training arms with handgrip training however this risk is minimal if the exercise is properly performed. The blood pressure and blood flow measurement procedures are non-invasive but you may experience numbness and/or tingling in the limb with the cuff(s) while we are taking our measurements. The gel used to image your heart and/or the sticker-electrodes used to measure your heart rate may cause a skin irritation however, this risk is minimal.

The insertion of a needle for blood sampling is common practice and involves few risks. There is local yet transient discomfort with the insertion of the needle, and there is a theoretical risk of infection, however blood draws will be made under completely sterile conditions. After we take out this needle, we will press firmly on the skin to minimize bruising.
Microneurography has been shown to be a safe method for measuring sympathetic nerve traffic to muscle. Microneurography has been used in laboratories all over the world with only 3 complications in the last 40 years, the worst of which was a slight weakness of the muscle of the leg lasting 2 to 6 months. You may notice a mild ache in the muscles of the right leg for a few days after the procedure.

Please contact one of the study investigators if you feel any adverse effects from completing any portion of the study, and/or if you have any questions or concerns. Exercise leaders and study investigators will reinforce proper training technique throughout the study intervention period. If you experience any adverse effects during any testing procedure, first line response will be provided.

POTENTIAL BENEFITS TO SUBJECTS AND/OR TO SOCIETY

You may or may NOT experience a lower blood pressure at rest or during your activities of daily life after each part of the study. In addition, you may or may not have improvements in the ability of your heart to vary its rhythm, a decrease in the activity of your nervous system, reduced tension in the blood vessels of your neck, an increase in the efficiency of the work of your heart, and/or reduced oxidative stress.

If we prove our theories, isometric handgrip training may be a possible prevention and/or treatment option for post-menopausal women, like you.

PAYMENT FOR PARTICIPATION

You will receive a Human Kinetics T-shirt for your participation, and will be reimbursed for parking costs over the course of the 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 your confidentiality, following your consent, you will be assigned an identification number. Your name will not be mentioned in any publication or presentation, and you will be identified with only your identification number on all collection tools (electronic or otherwise). All paper data and all electronic data will be stored in the locked laboratory (PACR Lab, Room #240, Human Kinetics Building, University of Windsor) of the study investigators. Information stored on computer will be password-accessible only. With respect to final disposal, all paper records (including medical and physical activity readiness 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 wish to answer and still remain in the study. The investigator may withdraw
you from this research if circumstances arise which warrant doing so (e.g., medication, nutrition and/or physical activity change).

FEEDBACK OF THE RESULTS OF THIS STUDY TO THE SUBJECTS

You 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 (http://www.uwindsor.ca/reb) at the completion of the study.

SUBSEQUENT USE OF DATA

This data may be used in subsequent studies however your privacy will be upheld with the use of your unique subject identification number under all circumstances.

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 April 2009
Appendix M: McMaster University Consent Form
A Study investigating the effects of isometric handgrip training on arterial blood pressure in post-menopausal women

Investigators: Michael Gregory, MHK Candidate; Dr. Maureen MacDonald, PhD; Dr. Cheri McGowan, PhD; Dr. Kevin Milne, PhD

Principal Investigator: Michael Gregory
Department of Kinesiology
University of Windsor
Windsor, Ontario, Canada
(519) 253-3000 ext. 2541
E-mail: (gregorym@uwindsor.ca)

Student Investigator:

Co-Investigator(s):
Dr. Cheri McGowan
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Windsor, Ontario, Canada
(519) 253-3000 ext. 2451
Email: (mcgowanc@uwindsor.ca)

Dr. Kevin Milne
Department of Kinesiology
University of Windsor
Windsor, Ontario, Canada
(519) 253-3000 ext. 2452
Email: (kjmilne@uwindsor.ca)

Faculty Supervisor:
Dr. Maureen MacDonald
Department of Kinesiology
McMaster University
Hamilton, Ontario, Canada
(905) 525-9140 ext. 23580
Email: (macdonmj@mcmaster.ca)

Research Sponsor: Canadian Institutes of Health Research – University of Windsor (Tri-Success Grant #: ORS-ERSO 29381)

Purpose of the Study

After menopause, women are at high risk of developing high blood pressure and heart disease. This study tests the theory that in post-menopausal women with and without high blood pressure, a simple form of exercise training, isometric handgrip training, will lower blood pressure at rest and during activities of daily life. Our study also tests the theory that this type of training will quiet the nervous system. In addition, we expect that the tension in the arteries of your neck, and/or the efficiency of your heart will be improved.

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

**Inclusion Criteria/Informed Consent/Familiarization Procedures**

**Visit 1 (30 minutes):**

After expressing interest in the study, if you meet the study’s qualifications, you will be invited to meet the investigators at the Cardiovascular and Dynamics Laboratory (Room #E102, Ivor Wynne Centre, McMaster University). At that time, you will be asked to read the consent form and information sheet on the study. After meeting with the study investigators, you will be shown 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 sign the informed consent, you will fill out a short medical questionnaire, and a physical activity (PARmed-X) questionnaire which you will take to your health care provider for him or her to complete. We encourage you to ask any questions related to the study at this time.

**Visit 2 (1 hour):**

After agreeing to participate in the study, and if you are eligible, you will undergo a practice test visit. We will let you practice all portions of the investigation (e.g., measurement of blood pressure and heart rate).

**Measurement Procedures - 3rd visit to completion of investigation:**

You will undergo the first testing session in the Cardiovascular and Dynamics Lab (Room #E102, Ivor Wynne Centre, McMaster University). To minimize outside factors on our measures, you will be asked to not have alcohol and to not exercise vigorously for 24-hours before each testing session. You will also be asked to avoid caffeine for 12-hours before the tests. All testing will take place at the same time of day, in a quiet, temperature-controlled room. On testing days, you will be asked to empty your bladder as a full bladder can increase blood pressure.

**Testing Days 1 and 2 (approximately 0.5 hours):** Your resting blood pressure will be measured in your upper arm after 10 minutes of seated rest. Your blood pressure will be measured 4 times, with 2-minutes of rest between measures. This will repeated again at least 24-hours after Testing Day 1.

**If you are still eligible to be in the study, the following testing days will occur:**

**Testing Day 3 (approximately 2 hours):** Upon arrival at the lab, your resting blood pressure will be measured after 10 minutes of seated rest, in the same way that is was
measured during Testing Days 1 and 2. Your heart rate will be monitored as well, using 3 sticker-electrodes that will be placed on your chest. Your breathing frequency will be measured using a breathing belt placed around your chest.

A technique called microneurography will then be used to measure, just below your knee, impulses travelling in a nerve to your calf muscle. This procedure has 2 parts. First, the position of your nerve will be mapped out using a pen-shaped instrument that emits a small electrical pulse. This will cause the muscles in your lower leg to twitch or tingle. This will be a strange sensation but will not be painful, and the sensations will disappear when the stimulation stops. A tiny, sterile wire electrode (about the size of a large human hair) will then be inserted through your skin and positioned just under the skin about 2-3 centimetres from the nerve site. This will be followed by the placement of a second tiny electrode, through your skin, into the nerve. The second electrode will be moved around, until the appropriate recording site is found. The electrode will remain in the nerve throughout the experiment. In most people, a satisfactory recording may be obtained after 20-30 minutes, but in some people, a good site cannot be found, or nerve activity is so low we cannot tell whether the best site has been found. If a good site cannot be located within 45 minutes, the procedure will stop. Once a proper recording site is obtained, your heart rate, blood pressure, breathing rate and nerve impulses will be recorded continuously for about 10 minutes. This technique will only be performed by a trained and actively practicing microneurographer (Dr. Phil Millar, McMaster).

Next, we will measure the pressure of blood flowing through the carotid artery located in your neck, as well as the diameter of the vessel. While still lying down, a pencil-like probe will be placed gently against your carotid artery on the right side of your neck and held lightly for a total of 2 minutes. On the opposite side, an image of the diameter of this same artery will be taken using an ultrasound wand. We will then use ultrasound to measure the amount of blood pumped from your heart, by holding a smaller ultrasound wand over your heart and in the notch above your breast bone.

At the end of the testing session, we will send you home with a device that will record your blood pressure for the next 24 hours. The morning following, you will return this device to the lab (Cardiovascular and Dynamics Lab, Room #E102, Ivor Wynne Centre, McMaster University).

Following baseline testing, you will be assigned, at random (by chance), to an isometric handgrip training group or a sham training group. If you are randomized to the isometric handgrip training group, you will train 3 times per week, for a total of 8 weeks. You will perform 4, 2-minute squeezes at 30% of your maximum squeeze, using both hands (each separated by 1 minute of rest) on a computerized handgrip. If you are randomized to the sham training group, you will perform 4, 2-minute squeezes at 3% (instead of 30%) of
your maximum squeeze. All training sessions per week will take place under the supervision of an exercise trainer, where your resting blood pressure will be measured before each session. Training sessions should not last longer than 30 minutes. Your exercise, nutritional, and medication status (where necessary) will be monitored throughout the study to make sure they do not change. Your health care provider will also be informed of the importance of keeping exercise, nutrition and medication status unchanged throughout the investigation, with the request of notifying one of the study investigators if one or more of these variables change.

At the end of the 8-weeks, all baseline tests will be repeated.

**Potential Harms, Risks or Discomforts:**

You may experience tendonitis in the tendons of the training arms with handgrip training however this risk is minimal if the exercise is properly performed. The blood pressure and blood flow measurement procedures are non-invasive but you may experience numbness and/or tingling in the limb with the cuff(s) while we are taking our measurements. The gel used to image your heart and/or the sticker-electrodes used to measure your heart rate may cause a skin irritation however, this risk is minimal.

Microneurography has been shown to be a safe method for measuring sympathetic nerve traffic to muscle. Microneurography has been used in laboratories all over the world with only 3 complications in the last 40 years, the worst of which was a slight weakness of the muscle of the leg lasting 2 to 6 months. You may notice a mild ache in the muscles of the right leg for a few days after the procedure. As this technique involves the insertion of a small electrode through the skin, there is a theoretical risk of infection at the site involved; however, the site is sterilized with the use of iodine and alcohol (99%) prior to the insertion and following the removal of the electrode from the location. Furthermore, the electrodes are all individually packaged and sterilized through the use of an autoclave as well, and no electrodes are ever recycled or reused.

Please contact one of the study investigators if you feel any adverse effects from completing any portion of the study, and/or if you have any questions or concerns. Exercise leaders and study investigators will reinforce proper training technique throughout the study intervention period. If you experience any adverse effects during any testing procedure, first line response will be provided.

**Potential Benefits**

You may or may NOT experience a lower blood pressure at rest or during your activities of daily life after each part of the study. In addition, you may or may not have a decrease
in the activity of your nervous system, reduced tension of the blood vessels of your neck, and/or an increase in the efficiency of the work of your heart.

If we prove our theories, isometric handgrip training may be a possible prevention and/or treatment option for high blood pressure in post-menopausal women, like you.

Payment or Reimbursement

All parking costs will be reimbursed, (excluding parking violations).

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 your confidentiality, following your consent, you will be assigned an identification number. Your name will not be mentioned in any publication or presentation, and you will be identified with only your identification number on all collection tools (electronic or otherwise). All paper data and all electronic data will be stored in the locked laboratory Cardiovascular and Dynamics Laboratory – Room #E102, Ivor Wynne Centre, McMaster University) of the study investigators. Information stored on computer will be password-accessible only. With respect to final disposal, all paper records (including medical and physical activity readiness questionnaires) will be shredded and all electronic data will be erased (formatted).

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 wish to answer and still remain in the study. The investigator may withdraw you from this research if circumstances arise which warrant doing so (e.g., medication, nutrition and/or physical activity change).

Information about the Study Results

If you would like to receive the summary personally, please let me know how you would like me to send it to you. This data may be used in subsequent studies however your privacy will be upheld with the use of your unique subject identification number under all circumstances.

Questions about the Study

If you have questions or need more information about the study itself, please contact: Dr. Maureen MacDonald: macdonmj@mcmaster.ca, 905-525-9140 ext. 23580 and/or Michael Gregory: gregorym@uwindsor.ca, 905-525-9140 ext. 27037.
This study has been reviewed by the Hamilton Health Sciences/Faculty of Health Sciences Research Ethics Board and has received ethics clearance.

If you have concerns or questions about your rights as a participant or about the way the study is conducted, please contact the Office of the Chair of the HHS/FHS REB at 905-521-2100, Ext. 42013.

CONSENT

I have read the information presented in the information letter about a study being conducted by the LPI, Dr. Maureen MacDonald of McMaster University, Master’s student Michael Gregory, and co-investigators Drs. Cheri McGowan and Kevin Milne, of the University of Windsor.

I have had the opportunity to ask questions about my involvement in this study and to receive additional details I requested.

I understand that if I agree to participate in this study, I may withdraw from the study at any time. I have been given a copy of this form. I agree to participate in the study.

Signature: ______________________________________

Name of Participant (Printed) ___________________________________

Date:  __________________________________

Name of Investigator (Printed): ___________________________________

Signature: ______________________________________

Date:  __________________________________

1. ...Yes, I would like to receive a summary of the study’s results.

   Please send them to this email address

   ____________________________________________

   or to this mailing address:

   ____________________________________________

   ... No, I do not want to receive a summary of the study’s results.

3. I agree to be contacted about a follow-up interview, and understand that I can always decline the request.
... Yes. Please contact me at: ________________________________

... No.
Appendix N: Medical Questionnaire

Last Name__________________________________ First Name _________________________________________
Address___________________________________________  City _________   Province_______________________
Sex (please circle):  M     F                               Height: ___________________   Weight:_______________________
Date of Birth ______________________Home Phone #   ( )______________  Postal Code_______________

FOR EMERGENCY NOTIFY:  Name______________________________   Relationship_______________________
Address_____________________________________________________      Phone____________________________
Family Doctor's Name______________________________________             Date of Last Physical________________

Please Check Yes or No:                                                                                                                                     Yes  No
1. Have you ever been hospitalized? ................................................................. □ □
   If yes, please specify?

Have you ever had surgery? ........................................................................ □ □
   If yes, please specify?

2. Are you presently taking any medications or pills? .......................... □ □
   If yes, please specify?

Are you presently taking any vitamins or supplements? ................... □ □

3. Do you have any allergies (medicine, bees or other stinging insects) .............................................................. □ □
   If yes, please specify?

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

Have you ever been told that you have a heart murmer? ................... □ □

Have you ever had racing of your heart or skipped heartbeats? .......... □ □

Has anyone in your family died of heart problems or a sudden death before age 50? □ □

5. Do you have any skin problems (itching, rashes, acne) ................ □ □

6. Do you have Diabetes? ............................................................... □ □

7. Do you have Asthma? ........................................................................ □ □

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

9. Have you had any other medical problems (infectious mononucleosis, etc.)? .................................................. □ □

10. Have you had any medical problems since your last physical? .................. □ □

11. Have you had any unexplained weight change? .............................................. □ □

12. Do you smoke? .................................................................................. □ □

13. Are you postmenopausal? ................................................................. □ □
   If yes, please specify?

Please explain any physical limitations that may prevent you from completing this study:
Appendix O: Physical Activity Readiness Medical Examination Questionnaire
M.H.K. Thesis – M. Gregory  Windsor – Applied Human Performance

The PARmed-X is a physical activity-specific checklist to be used by a physician with patients who have had positive responses to the Physical Activity Readiness Questionnaire (PAR-Q). In addition, the Conveyance/Referral Form in the PARmed-X can be used to convey clearance for physical activity participation, or to make a referral to a medically-supervised exercise program.

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. The PAR-Q by itself provides adequate screening for the majority of people. However, some individuals may require a medical evaluation and specific advice (exercise prescription) due to one or more positive responses to the PAR-Q.

Following the participant’s evaluation by a physician, a physical activity plan should be devised in consultation with a physical activity professional (CSEP-Professional Fitness & Lifestyle Consultant or CSEP-Exercise Therapist™). To assist in this, the following instructions are provided:

PAGE 1: Sections A, B, C, and D should be completed by the participant BEFORE the examination by the physician. The bottom section is to be completed by the examining physician.

PAGES 2 & 3: A checklist of medical conditions requiring special consideration and management.

PAGE 4: Physical Activity & Lifestyle Advice for people who do not require specific instructions or prescribed exercise.

- Physical Activity Readiness Conveyance/Referral Form - an optional tear-off tab for the physician to convey clearance for physical activity participation, or to make a referral to a medically-supervised exercise program.

This section to be completed by the participant

A PERSONAL INFORMATION:

NAME ___________________________

ADDRESS ___________________________

TELEPHONE ___________________________

BIRTHDATE __________ GENDER ______

MEDICAL No. _________________________

This section to be completed by the examining physician

C RISK FACTORS FOR CARDIOVASCULAR DISEASE:

Check all that apply:

- Less than 30 minutes of moderate physical activity most days of the week.
- Currently smoker (tobacco smoking 1 or more times per week).
- High blood pressure reported by physician after repeated measurements.
- High cholesterol level reported by physician.
- Excessive accumulation of fat around waist.
- Family history of heart disease.

Please note: Many of these risk factors are modifiable. Please refer to page 4 and discuss with your physician.

Physical Exam:

Ht Wt BPI /  / BPI /

Conditions limiting physical activity:

- Cardiovascular
- Respiratory
- Musculoskeletal
- Abdominal
- Other

Tests required:

- ECG
- Blood
- Exercise Test
- Urinalysis
- X-Ray
- Other

Further Information:

- Attached
- To be forwarded
- Available on request

Physical Activity Readiness Conveyance/Referral:

Based upon a current review of health status, I recommend:

- No physical activity
- Only a medically-supervised exercise program until further medical clearance
- Progressive physical activity:

- with avoidance of:
- with inclusion of:

- under the supervision of a CSEP-Professional Fitness & Lifestyle Consultant or CSEP-Exercise Therapist™
- Unrestricted physical activity–start slowly and build up gradually

Supported by: Canada Canada

© Canadian Society for Exercise Physiology

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**PARmed-X**

**PHYSICAL ACTIVITY READINESS MEDICAL EXAMINATION**

Following is a checklist of medical conditions for which a degree of precaution and/or special advice should be considered for those who answered "YES" to one or more questions on the PAR-Q, and people over the age of 60. Conditions are grouped by system. Three categories of precautions are provided. Comments under Advice are general, since details and alternatives require clinical judgement in each individual instance.

<table>
<thead>
<tr>
<th>Absolute Contraindications</th>
<th>Relative Contraindications</th>
<th>Special Prescriptive Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Permanent restriction or temporary restriction until condition is treated, stable, and/or past acute phase.</td>
<td>Highly variable. Value of exercise testing and/or program may exceed risk. Activity may be restricted.</td>
<td>Individually prescriptive advice generally appropriate:</td>
</tr>
<tr>
<td></td>
<td>Desirable to maximize control of condition. Direct or indirect medical supervision of exercise program may be desirable.</td>
<td>- Limitations imposed; and/or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Special exercises prescribed.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May require medical monitoring and/or initial supervision in exercise program.</td>
</tr>
</tbody>
</table>

**ADVICE**

- Clinical exercise test may be warranted in selected cases, for specific determination of functional capacity and limitations and precautions at any.
- Slow progression of exercise to levels based on test performance and individual tolerance.
- Consider individual need for initial conditioning program under medical supervision (indirect or direct).

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute disseminated</td>
<td>Acute myocardial infarction (acute)</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Acute coronary syndrome (moderate)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>Acute ischemic heart syndrome</td>
<td></td>
</tr>
<tr>
<td>Aortic stenosis (moderate)</td>
<td>Acute pulmonary stenosis</td>
<td></td>
</tr>
</tbody>
</table>

**Infections**

- Acute infectious disease (regardless of etiology)
- Subacute/thrombocytopenic infectious diseases (e.g., malaria, others)

**Metabolic**

- Uncontrolled metabolic disorder (diabetes mellitus, thyrotoxicosis, myxedema)
- Renal, hepatic, and/or metabolic insufficiency
- Obesity
- Single kidney

**Pregnancy**

- Complicated pregnancy (e.g., toxemia, hemorrhage, incompetent cervix, etc.)
- Advanced pregnancy (late third trimester)

References:


The PAR-Q and PARmed-X were developed by the British Columbia Ministry of Health. They have been reviewed by an Expert Advisory Committee of the Canadian Society for Exercise Physiology chaired by Dr. N. G. (2002).

No changes permitted. You are encouraged to photocopy the PARmed-X, but only if you use the entire form.

Disponible en français sous le titre «Évaluation médicale de l’aptitude à l’activité physique (X-AAP)».
### Special Prescriptive Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Advice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>special relaxation and breathing exercises</td>
</tr>
<tr>
<td></td>
<td>breath control during endurance assessment to tolerance; avoid polluted air</td>
</tr>
<tr>
<td>Asthma</td>
<td>avoid hyperhydration during exercise; avoid extremely hot conditions; warm up adequately; utilize appropriate medication.</td>
</tr>
<tr>
<td>Arthritis—acute (infectious, rheumatoid; gout)</td>
<td>treatment, plus judicious blend of rest, splinting and gentle movement</td>
</tr>
<tr>
<td>Arthritis—subacute</td>
<td>progressive increase of active exercise therapy</td>
</tr>
<tr>
<td>Arthritis—chronic (osteoarthritis and above conditions)</td>
<td>maintenance of mobility and strength; non-weightbearing exercises to minimize joint trauma (e.g., cycling, aquatic activity, etc.)</td>
</tr>
<tr>
<td>Obesity</td>
<td>highly variable and individualized</td>
</tr>
<tr>
<td>Anemia</td>
<td>minimize straining and isotonic stresses; strengthen abdominal muscles</td>
</tr>
<tr>
<td>Coronary disorder not completely controlled by medication</td>
<td>minimize or avoid exercise in hazardous environments and/or exercising alone (e.g., swimming, mountain climbing, etc.)</td>
</tr>
<tr>
<td>Recent concussion</td>
<td>thorough examination if history of two concussions; review for discontinuation of contact sport if three concussions, depending on duration of unconsciousness, retrograde amnesia, persistent headaches, and other objective evidence of cerebral damage</td>
</tr>
<tr>
<td>Anemia—severe (≤ 10 G/dL)</td>
<td>control preferred; exercise as tolerated</td>
</tr>
<tr>
<td>Electrolyte disturbances</td>
<td>control preferred; exercise as tolerated</td>
</tr>
<tr>
<td>Angina</td>
<td>potential for ischemic syncope, arrhythmias, imbalance, bradycardia, dysrhythmias, impaired coordination and reaction time, heat intolerance. May alter resting and exercise ECGs and exercise test performance.</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td>potential for ischemic syncope, arrhythmias, imbalance, bradycardia, dysrhythmias, impaired coordination and reaction time, heat intolerance. May alter resting and exercise ECGs and exercise test performance.</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>potential for ischemic syncope, arrhythmias, imbalance, bradycardia, dysrhythmias, impaired coordination and reaction time, heat intolerance. May alter resting and exercise ECGs and exercise test performance.</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>potential for ischemic syncope, arrhythmias, imbalance, bradycardia, dysrhythmias, impaired coordination and reaction time, heat intolerance. May alter resting and exercise ECGs and exercise test performance.</td>
</tr>
<tr>
<td>Diuretics</td>
<td>potential for ischemic syncope, arrhythmias, imbalance, bradycardia, dysrhythmias, impaired coordination and reaction time, heat intolerance. May alter resting and exercise ECGs and exercise test performance.</td>
</tr>
<tr>
<td>Others</td>
<td>potential for ischemic syncope, arrhythmias, imbalance, bradycardia, dysrhythmias, impaired coordination and reaction time, heat intolerance. May alter resting and exercise ECGs and exercise test performance.</td>
</tr>
</tbody>
</table>

*Note to physical activity professionals... It is a prudent practice to retain the completed Physical Activity Readiness Questionnaire/Referral Form in the participant's file.
PARmed-X PHYSICAL ACTIVITY READINESS MEDICAL EXAMINATION

Physical activity improves health.

Every little bit counts, but none is even better – everyone can do it!

Get active your way: - build physical activity into your daily life... 
- at home
- at school
- at work
- at play
- on the way

That’s active living!

Starting slowly is very safe for most people. Not sure? Consult your health professional.


Eating well is also important. Follow Canada’s Food Guide for healthy eating to meet your basic food needs.

Benefits of regular activity: health risks of inactivity:
- Lower risk of heart disease and stroke
- Lower risk of type II diabetes
- Stronger muscles and bones
- Weight control
- Stronger immune system
- Better mental health
- Better sleep and sense of well-being
- Continues independent living in own home
- Bone cancer
- Breast cancer
- Colon cancer
- Other cancers
- Diabetes
- Asthma

For more information on physical activity benefits and risks, check the website www.cancer.ca/physicalactivity

Parmed-X Physical Activity Readiness Conveyance/Referral Form

Based upon a current review of the health status of ____________________________, I recommend:

- No physical activity
- Only a medically-supervised exercise program until further medical clearance
- Progressive physical activity
  - with avoidance of: ____________________________
  - with inclusion of: ____________________________
  - under the supervision of a CSEP-Professional Fitness & Lifestyle Consultant or CSEP-Exercise Therapist™
- Unrestricted physical activity — start slowly and build up gradually

__________________________________________________________________________

M.D.

_________________________ (date)

FURTHER INFORMATION:
- Attached
- To be forwarded
- Available on request

NOTE: This physical activity clearance is valid for a maximum of six months from the date it is completed and becomes invalid if your medical condition becomes worse.

Physician/clinic stamp:
Appendix P: University of Windsor Health Care Provider Documents
Dear Dr. ________________,

Your patient, ________________________________, has expressed interest in participating in our research study in the Department of Kinesiology at the University of Windsor entitled: Isometric handgrip training and arterial blood pressure in post-menopausal women (see attached Letter of Information for Consent for details). If you approve your patient’s participation in our study (via Parmed-X), we kindly request that you or a representative inform us of any changes in medically-endorsed exercise, nutrition or medication status, as these changes may influence our findings. We ask that you sign the attached form for return with the PARmed-X to acknowledge receipt of this request.

Thank-you for your help, and we appreciate your support. Please do not hesitate to contact us if you have any questions or concerns.

Sincerely,

Drs. Cheri McGowan and Kevin Milne
Assistant Professors
Department of Kinesiology
Faculty of Human Kinetics
University of Windsor
Dear Drs. McGowan and Milne,

I, ________________________________, acknowledge that my patient __________________________ has expressed interest in participating in our research study in the Department of Kinesiology at the University of Windsor entitled: Isometric handgrip training and arterial blood pressure in post-menopausal women. I have approved my patient’s participation in your study (via Parmed-X), and I, or one of my representatives, will inform you of any changes in medically-endorsed exercise, nutrition or medication status.

Date: ____________________________

____________________________
Appendix Q: McMaster University Health Care Provider Documents
Date: ________________.

Dear Dr. __________________,

Your patient, ________________________________, has expressed interest in participating in our research study in the Department of Kinesiology at McMaster University, entitled: Isometric handgrip training and arterial blood pressure in post-menopausal women (see attached Letter of Information for Consent for details). If you approve your patient’s participation in our study (via Parmed-X), we kindly request that you or a representative inform us of any changes in medically-endorsed exercise, nutrition or medication status, as these changes may influence our findings. We ask that you sign the attached form for return with the PARmed-X to acknowledge receipt of this request.

Thank-you for your help, and we appreciate your support. Please do not hesitate to contact us if you have any questions or concerns.

Sincerely,

Dr. Maureen MacDonald
Professor
Department of Kinesiology
Faculty of Human Kinetics
McMaster University
Dear Dr. MacDonald,

I, ________________________________, acknowledge that my patient __________________________ has expressed interest in participating in our research study in the Department of Kinesiology at McMaster University entitled: Isometric handgrip training and arterial blood pressure in post-menopausal women. I have approved my patient’s participation in your study (via Parmed-X), and I, or one of my representatives, will inform you of any changes in medically-endorsed exercise, nutrition or medication status.

____________________________________
Appendix R: Training Log
## TRAINING LOG:

**Participant ID: ________________________________**

<table>
<thead>
<tr>
<th>Date</th>
<th>What was your maximum voluntary contraction value? Right_{max} &amp; Left_{max}</th>
<th>Did you complete two sets with each hand? (% at end of session)</th>
<th>Have you had any new medications prescribed to you and/or have you started taking any new products?</th>
<th>Have you had any significant dietary changes? If yes, please describe.</th>
<th>Have you had any physical activity changes? If yes, please describe.</th>
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**Please Note:**
- A change in diet is any abnormal addition or subtraction of calories or foods
- A change in medication is any addition or subtraction of medications (i.e. change)
- A change in physical activity is the addition or subtraction of a structured physical activity program
Appendix S: University of Windsor PACR Lab Emergency Action Plan

EMERGENCY ACTION PLAN (EAP)
FOR **MEDICAL EMERGENCIES** DURING EXERCISE TESTING

**STEP 1:**

REMAIN CALM.

CONTROL and ASSESS the situation.

DESIGNATE a person to CALL and meet EMERGENCY PERSONNEL:

Campus Police EXT. 4444 OR 911

(they will dispatch required authorities)

**OUR ADDRESS/DIRECTIONS:**

The University of Windsor

Human Kinetics Building

2555 College Ave.

Main Entrance off College Ave.

Room# 240 (uppermost floor)

Go in through the main doors of the Human

**STEP 2:**

PERFORM all measures (CPR/First Aid) to ensure safety of subject.

ATTEND to subject until replaced by emergency personnel.
Appendix T: McMaster University Vascular Dynamics Lab Emergency Action Plan
F. Emergency Procedures / Contacts

- For fire/life emergencies, personnel are to call 88 and proceed with the emergency procedures as directed.
- All personnel must be familiar with the locations of, and procedures for using, an eyewash fountain, safety shower, fire extinguisher, an emergency alarm and telephone.
- In case of evacuation, all personnel must be familiar with the main and alternate evacuation routes. (Note: In the event of an evacuation, you must contact your supervisor or health and safety representative in order to let him/her know you are safe.)
- Emergency telephone is located in the E102 A.
- **In the event of an emergency**, assistance will be provided by:
  - McMaster Campus Security **ext. 88**
  - Environmental & Occupational Health Support Services **ext. 24352**
Vita Auctoris
Michael Andrew Gregory was born during the fall of 1986 in Chatham, Ontario to Richard and Jean Gregory. Mike graduated from John McGregor Secondary School in 2004. Following high school, Mike completed a Bachelor of Science degree at the University of Guelph in 2009. Following his undergraduate studies, Mike earned a Master’s of Human Kinetics degree at the University of Windsor in 2012. Mike plans to pursue a PhD in Health and Rehabilitation Sciences at Western University in fall 2012.