8-4-2017

Isometric handgrip training-induced reductions in blood pressure: The influence of age and cardiovascular reactivity as an outcome predictor in normotensive women

Mary Ann Zokvic
University of Windsor

Isometric handgrip training-induced reductions in blood pressure: The influence of age and cardiovascular reactivity as an outcome predictor in normotensive women

by
Mary Ann Zokvic

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

Windsor, Ontario, Canada

Isometric handgrip training-induced reductions in blood pressure: The influence of age and cardiovascular reactivity as an outcome predictor in normotensive women

by

Mary Ann Zokvic

APPROVED BY:

_____

C. Abeare
Department of Psychology

_____

I. Swaine
Department of Kinesiology

_____

K. Milne, Co-Advisor
Department of Kinesiology

_____

C. McGowan, Co-Advisor
Department of Kinesiology

July 12th 2017

Declaration of Co-Authorship / Previous Publication

I. Co-Authorship Declaration

I hereby declare that this thesis incorporates material that is result of joint research, as follows: *This thesis also incorporates the outcome of research undertaken by Ms. Yasina Somani under the supervision of Dr. Cheri McGowan. The collaboration is covered in Chapter 2 of the thesis. In all cases, the key ideas, primary contributions, experimental designs, data analysis and interpretation, were performed by Ms. Mary Ann Zokvic, and the contribution of co-authors was through collection of data in the younger participant cohort.*

I am aware of the University of Windsor Senate Policy on Authorship and I certify that I have properly acknowledged the contribution of other researchers to my thesis, and have obtained written permission from each of the co-author(s) to include the above material(s) in my thesis.

I certify that, with the above qualification, this thesis, and the research to which it refers, is the product of my own work.

II. Declaration of Previous Publication

This thesis includes a small subset of data from the young normotensive cohort recruited for Ms. Yasina Somani's graduate thesis (MHK; University of Windsor).

Thesis Chapter	Publication title/full citation	Publication status*
Chapter 2	Somani, Y.B. (2015). The effect of a 10 week isometric handgrip training protocol on blood pressure (resting and ambulatory) and cardiovascular reactivity in young, normotensive individuals. *Electronic Theses and Dissertations.* 5285.	*Published*

I certify that I have obtained a written permission from the copyright owner(s) to include the above published material(s) in my thesis. I certify that the above material describes work completed during my registration as graduate student at the University of Windsor.

I declare that, to the best of my knowledge, my thesis does not infringe upon anyone's copyright nor violate any proprietary rights and that any ideas, techniques, quotations, or any other material from the work of other people included in my thesis, published or otherwise, are fully acknowledged in accordance with the standard referencing practices. Furthermore, to the extent that I have included copyrighted material that surpasses the bounds of fair dealing within the meaning of the Canada Copyright Act, I certify that I have obtained a written permission from the copyright owner(s) to include such material(s) in my thesis.

I declare that this is a true copy of my thesis, including any final revisions, as approved by my thesis committee and the Graduate Studies office, and that this thesis has not been submitted for a higher degree to any other University or Institution.

Abstract

The World Health Organization has identified hypertension (HTN) as a global health crisis and emphasizes primary prevention as the key to mitigating HTN-related morbidity and mortality. Hypertension Canada and the American Heart Association promote isometric handgrip (IHG) exercise as an adjuvant therapy for controlling blood pressure (BP). Coupling IHG training with a method for identifying responders to this intervention would strengthen its use as a tool for the primary prevention of HTN. The aim of this prospective study was to determine whether systolic BP reactivity to a stress task (i.e. IHG task, IHGT; serial subtraction task, SST) is predictive of IHG training-induced BP adaptations in both young and older normotensive women. Following 10 weeks of IHG training, significant and equal reductions in resting systolic BP were observed in both young (n = 7) and older women (n = 7, $P < 0.05$). Concomitant reductions in 24 hour and daytime ambulatory systolic BP were also observed in both cohorts (n = 5 older, n = 7 young, $P < 0.05$). Systolic BP reactivity to the IHGT, but not the SST, was predictive of 24 hour ambulatory systolic BP reductions in older women only (n = 5, $P < 0.05$). These findings support the use of IHG training as a primary HTN prevention tool in both young and older normotensive women. Moreover, although preliminary, these findings suggest that systolic BP reactivity to an IHGT may be used to identify responders to IHG training for the purpose of prescribing IHG exercise in older women.

Acknowledgements

The completion of this thesis would not have been possible without support and guidance from the following remarkable individuals.

Thank you to my co-advisors, Drs. Cheri McGowan and Kevin Milne, for helping me circumnavigate the challenges of graduate school and research. With your guidance I have become a better scholar, more well-rounded individual, and conducted a research project I can be proud of.

Thank you to my committee members, Drs. Ian Swaine, and Christopher Abeare. Each of your unique perspectives and expertise were invaluable resources on this journey.

To all my PACR lab mates; you have made this experience a memorable one. Thank you for your kindness, collaboration and comedic relief. I'd especially like to acknowledge Yasina Somani and Michael Pearl for their contributions to this research. I will be fortunate to have peers like all of you in my future endeavors.

To my parents, family and friends; you have all played a vital role in raising me to stand where I do today. For your boundless love and support I am forever grateful.

Lastly, I'd like to thank the research participants who accompanied me on this pursuit of knowledge. I am proud to present to you the fruits of our labour…

Table of Contents

List of Tables

List of Figures

List of Appendices

List of Abbreviations

ACh - Acetylcholine

ACSM - American College of Sports Medicine

AHA - American Heart Association

ANP - Atrial Natriuretic Peptide

ANS - Autonomic Nervous System

ATP - Adenosine Triphosphate

AVP - Arginine Vasopressin

BMI - Body Mass Index

BP - Blood Pressure

CC - Central Command

CCC - Cardiovascular Control Center

CPT - Cold Pressor Task

CVD - Cardiovascular Disease

DASH - Adopting the Dietary Approach to Stop Hypertension

E - Epinephrine

EPR - Exercise Pressor Reflex

ET - Endothelin

IHG - Isometric Handgrip

IHGT - Isometric Handgrip Task

IL - Isometric Leg

HR - Heart Rate

HTN - Hypertension

MAP - Mean Arterial Blood Pressure

mmHg - Millimeters of Mercury

MSNA - Muscle Sympathetic Nerve Activity

MVC - Maximum Voluntary Contraction

NA^+/K^+ - Sodium/Potassium

NE - Norepinephrine

NO - Nitric Oxide

PEH - Post-Exercise Hypotension

PNS - Parasympathetic Nervous System

PP - Pulse Pressure

Q - Cardiac Output

RAAS - Renin Angiotensin Aldosterone System

SA - Sinoatrial

SD - Standard Deviation

SE - Standard Error

SNS - Sympathetic Nervous System

SST - Serial Subtraction Task

SV - Stroke Volume

TPR - Total Peripheral Resistance

WHO - World Health Organization

Chapter 1: Introduction and Literature Review

1.1 Cardiovascular Disease

As a result of advances in healthcare, together with an older population, many humans are living longer with one or more chronic diseases (WHO, 2013). Non-transmissible diseases such as cardiovascular disease (CVD) have surpassed infectious diseases as the leading cause of mortality worldwide (WHO, 2013). CVD is a broad term that encompasses all disorders of the human heart and vasculature, including conditions such as stroke, atherosclerosis, cardiac arrest, arrhythmia, endocarditis and coronary heart disease (WHO, 2013).

CVD is the number one global cause of death. In 2008, CVD accounted for 17.3 million deaths and this number is projected to increase to 23.3 million deaths in the year 2030 (WHO, 2013). Fortunately, due to advancements in treatment many individuals who may have died from CVD are able to live with the disease. Consequently, the persistence of individuals with CVD poses strains on the economy. In Canada, coronary heart disease, stroke, and heart disease due to high blood pressure incur $21 billion in expenses to provide medication, hospitalization and disability compensation (Theriault et al., 2010). Individuals living with CVD often miss work due to hospitalization and experience lower productivity than non-afflicted individuals (Theriault et al., 2010). In addition, patients living with CVD experience a significant reduction in their quality of life due to the strain of coping with illness (Juenger et al., 2002). Accordingly, the World Health Organization (WHO) has deemed CVD a global health crisis with emphasis on primary prevention as the key to slowing its deadly progression (WHO, 2013).

There are a variety of behavioural and physiological factors that increase an individual's risk of developing CVD. These include smoking, alcohol consumption,

physical inactivity, obesity, high cholesterol, diabetes, and hypertension (Beevers et al., 2001).

1.2 Hypertension

Hypertension (HTN), or chronically sustained elevations in arterial blood pressure (BP), is considered the strongest prognostic indicator of CVD (Schillaci et al., 2009). Regulation of BP is required to ensure efficient function of the cardiovascular system and adequate perfusion of bodily tissues by blood flow (Herd, 1970). BP represents the force exerted by blood on the vasculature and comprises both systolic BP and diastolic BP measures (Herd, 1970). Systolic BP represents the force exerted during the contractile phase of the cardiac cycle whereas diastolic BP represents the force exerted during the relaxation phase of the cardiac cycle (Herd, 1970). Normal resting BP values are defined as measures of systolic BP $\leq$ 120 mmHg and diastolic BP $\leq$ 80 mmHg (Leung et al., 2016). Individuals with resting systolic BP values ranging between 120-134 mmHg and/or resting diastolic BP values ranging between 80-84 mmHg are considered to have high-normal BP or preHTN (Leung et al., 2016; Myers et al., 2015). As the precursor to HTN development, preHTN is also a risk factor for CVD. A longitudinal study of normotensive and prehypertensive post-menopausal women showed prehypertensive women to be at a greater risk for myocardial infarction, stroke, heart failure and cardiovascular death (Hsia et al., 2007). HTN is defined as having automated office resting systolic BP $\geq$ 135 mmHg, and/or diastolic BP $\geq$ 85 mmHg, and/or taking anti-hypertensive medication (Leung et al., 2016; Myers et al., 2015; Chobanian et al., 2003). Automated office BP measurement is the preferred method of office BP measurement during which multiple BP measures are obtained in absence of a health care provider. In

contrast, HTN is defined by non-automated office measures as resting systolic BP $\geq$ 140 mmHg and/or diastolic BP $\geq$ 90 mmHg (Leung et al., 2016; Myers et al., 2015). HTN can be further classified into two stages where resting BP within the range of 140-159/90-99 mmHg is classified as Stage 1 and resting BP $\geq$ 160/100 mmHg is classified as Stage 2 (Myers et al., 2015; Weber et al., 2014). Ambulatory BP, which provides insight into 24 hour BP fluctuations, is a more accurate and superior prognostic indicator of CVD risk in comparison to clinical resting BP measures (Pickering et al., 2006; O'Brien et al., 2001). Using ambulatory BP measures, HTN is defined as awake BP $\geq$ 135/85 mmHg and/or 24 hour BP $\geq$ 130/80 mmHg (Leung et al., 2016).

HTN is classified as primary (essential) or secondary based on the cause. Secondary HTN occurs in the presence of other identifiable conditions such as renal or adrenal disorders, which directly produce sustained increases in BP (Carretero et al., 2000). In these cases, secondary HTN is reversed with the treatment of these associated disorders (Carretero et al., 2000). In contrast, primary HTN, described in detail below (Section 1.2.4 Pathophysiology of Hypertension), has no identifiable cause and concernedly accounts for 95% of all cases of HTN (Carretero et al., 2000). Although the cause of primary HTN remains elusive, it is likely related to dysfunction in the neural, hormonal and local pathways responsible for BP regulation (Carretero et al., 2000). Consequently, interventions for BP reduction and particularly primary HTN prevention are of utmost importance in combatting the fast growing CVD epidemic (WHO, 2013).

1.2.1 Regulation of Blood Pressure

Prior to discussing the pathophysiology of primary HTN, it is important to understand the mechanisms responsible for modulating the determinants of BP. BP is a

product of cardiac output (Q) and total peripheral resistance (TPR), where Q refers to the volume of blood pumped out of the heart per minute and TPR refers to the resistance to blood flow produced by all vasculature (Ackerman, 2004). Q is the product of heart rate (HR) and stroke volume (SV) (Ackerman, 2004). Changes in Q and TPR are controlled through numerous innate pathways including neural, hormonal, and local mechanisms, resulting in the manipulation of BP.

Neural Blood Pressure Control

BP is neurologically controlled through the activity of two branches of the autonomic nervous system (ANS): the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS). Sympathetic activity produces resistance to blood flow subsequently increasing TPR and BP as a result (Dampney et al., 2002). Sympathetic activity also increases HR and the force of myocardial contraction, causing an increase in Q, and subsequently BP. In contrast, parasympathetic activity leads to decreases in HR and myocardial contractility (Dampney et al., 2002). Therefore, the net effect of neural activity on BP is dependent on the balanced stimulation of these two systems.

The activity of the PNS and SNS is coordinated by two brain regions known as central command (CC) and the cardiovascular control center (CCC). The CCC receives information regarding ANS activity via innervation from the CC (Victor et al., 1995). The CCC then modulates the relative activity of the PNS and SNS around a homeostatic set-point. In addition to feed forward control, autonomic outflow (and thus BP) is modified based on feedback received by the CCC from receptors located in the periphery (i.e., negative feedback control systems). These peripheral sensory receptors include: arterial baroreceptors, chemoreceptors and muscle afferent receptors (Victor et al., 1995).

Arterial baroreceptors are stretch receptors located in the heart, pulmonary vessels and carotid artery where they sense conformational changes in vessel walls resulting from alterations in BP (Lafranchi & Somers, 2002). Increases in BP above a central set-point increase the frequency of afferent signalling from baroreceptors to the CCC causing increases in PNS activity whilst decreasing SNS activation (Lafranchi & Somers, 2002). Collectively, HR, Q and TPR are reduced which subsequently reverts BP to the central set-point. In contrast, decreases in BP reduce the frequency of signalling from baroreceptors to the CCC resulting in increased SNS activity and decreased PNS activation. Consequently, HR, Q and TPR are increased to raise BP to the central set-point (Lafranchi & Somers, 2002).

Chemoreceptors are located in the carotid and aortic arteries where they communicate decreases in the partial pressure of oxygen, increases in the partial pressure of carbon dioxide and increases in hydrogen ion concentration due to cellular respiration (Prabhakar, 2000). This information is relayed to the CCC via afferent feedback resulting in increased SNS activation. The response that follows includes increased TPR through vasoconstriction of vascular beds and increased ventilation. These responses serve to increase BP and oxygen uptake in order to maintain adequate tissue perfusion (Prabhakar, 2000).

Muscular afferent receptors that influence BP regulation include type III afferent mechanoreceptors and type IV afferent metaboreceptors. Type III receptors sense stretch and deformation in arteries caused by internal pressure changes in the artery (Leshnower et al., 2001). This information is relayed to the CCC which augments sympathetic outflow to produce increases in Q via increases in HR and consequently BP. Type IV receptors sense increases in the metabolic by-products of muscle contraction including: lactic acid,

dipronated phosphate, potassium, bradykinin, serotonin and adenosine (Leshnower et al., 2001). The CCC responds to this information by modulating SNS activity to increase Q via increases in HR and consequently BP (Leshnower et al., 2001).

Hormonal Blood Pressure Control

Hormonal modulators of BP include the catecholamines, epinephrine (E) and norepinephrine (NE), acetylcholine (ACh), the renin-angiotensin-aldosterone system (RAAS), arginine vasopressin (AVP), and atrial natriuretic peptide (ANP).

Secretion of E and NE from the adrenal glands is largely regulated by SNS activity through direct innervation of adrenal medullary cells by sympathetic neurons (Manneli et al., 1990). Whereas E is released directly into circulation, NE is released primarily at synaptic junctions between sympathetic nerve fibers and vascular beds. The cardiovascular effect of these catecholamines is also dependent on the receptor they bind to and their location in the body. There are two main classes of E and NE receptors: α-adrenergic and β-adrenergic. α_1-adrenergic receptors are located in most sympathetic target organs, excluding the heart whereas α_2-adrenergic receptors are located at the synaptic junction of SNS nerve endings at vascular beds. β_1-adrenergic receptors are located in the heart, lungs, kidneys and adipose tissue whereas β_2-adrenergic receptors are located in most sympathetic target organs such as the heart, eyes, kidney, brain, gastrointestinal tract and vascular smooth muscle (Manneli et al., 1990). Smooth muscle comprises the media layer of all vasculature and its contractility regulates blood vessel diameter. Contraction of the smooth muscle results in decreased vessel diameter (vasoconstriction) and relaxation results in increased vessel diameter (vasodilation) (Furchgott, 1983). When bound to an α_1 or α_2-adrenergic receptor, E and NE produce vasoconstriction versus vasodilation when bound to a β_2-adrenergic receptor (Manneli et

al., 1990). These modifications of smooth muscle diameter regulate BP through changes in TPR. Vasoconstriction produces an increase in TPR and subsequently BP whereas vasodilation decreases TPR and BP. When bound to β_1-adrenergic receptors in cardiac cells, E and NE accelerate the rate of impulse generation at the sinoatrial (SA) node of the heart, thereby increasing HR, Q, and consequently, BP (Larsson, 2010).

In contrast, PNS activity causes the release of the neurotransmitter ACh from parasympathetic nerve fibers. ACh binds to muscarinic receptors on cardiac cells where it reduces cardiac contractility and Q, thereby reducing BP. Furthermore, ACh can hyperpolarize the SA node which increases the time (refractory period) between cardiac contractions, lowering HR and therefore lowering BP (Brodde & Michel, 1999). Exogenous ACh can also activate muscarinic receptors on vascular endothelial cells causing increased synthesis of the vasodilator nitric oxide (NO), subsequently decreasing TPR and BP (Kellogg et al., 2005).

The RAAS system influences BP through its effects on blood fluid volume and vascular tone. Renin, a glycoprotein enzyme, is released from the kidneys and converts the liver pro-hormone angiotensinogen into angiotensin I (Nguyen et al., 2002). Angiotensin I is further modified by angiotensin converting enzyme into angiotensin II, the active form of the hormone. Angiotensin II is a vasoconstrictor that directly affects BP by increasing TPR (Nguyen et al., 2002). It also stimulates aldosterone release from the adrenal cortex, which promotes fluid retention through sodium conservation leading to an increase in blood fluid volume, SV, and ultimately BP (Hall et al., 1990).

The atria of the heart release ANP in response to increased BP causing cardiac muscle to stretch (Chen et al., 2008). ANP serves to reduce BP by promoting vasodilation in vascular smooth muscle through inhibition of actin-myosin binding thus decreasing

TPR. Secondly, ANP binds to membrane receptors on renal cells prompting the kidneys to excrete sodium and water. This reduces total blood fluid volume consequently reducing SV and ultimately BP (Chen et al., 2008). In contrast to ANP, AVP is released by the pituitary and serves to increase BP by causing vasoconstriction of vascular smooth muscle, which increases TPR, and by promoting water retention, which increases SV (Henderson & Bryon, 2007).

Local Blood Pressure Control

BP is regulated by locally released substances that are produced in response to the metabolic demands of tissues. These local regulators of BP include potassium, adenine derivatives, NO and endothelin (ET)-1, and their primary function is to change smooth muscle diameter, which modifies TPR and alters BP (Webb, 2003).

Potassium accumulates in the interstitial space surrounding arterioles as a by-product of muscle contraction and triggers increased activity of the sodium-potassium (Na^+/K^+) pump at the smooth muscle membrane (Haddy et al., 2006). This causes hyperpolarization of smooth muscle cells and subsequently decreases calcium influx into the cell (Haddy et al., 2006). As a result, smooth muscle vasoconstriction decreases, reducing TPR and decreasing BP.

Similarly, adenosine triphosphate (ATP) is an adenine derivative and key substrate in muscle contraction (Haddy & Scott, 1968). As ATP is catabolized to produce smooth muscle contractions, the by-products adenosine diphosphate, adenosine monophosphate, and adenosine accumulate. In order to increase blood flow and deliver the necessary substrates to the working muscle, these metabolites produce a vasodilatory response which decreases TPR, and ultimately BP (Haddy & Scott, 1968).

This increase in blood flow in response to muscle metabolism increases the force (shear stress) exerted by blood on the innermost layer of cells comprising the blood vessel wall known as the vascular endothelium, which stimulates NO production by these cells (Thijseen et al., 2011; Furchgott, 1983). NO is produced from L-arginine through the activity of the enzyme NO synthase. NO then diffuses from the endothelium where it interacts with vascular smooth muscle to produce a vasodilatory response, which decreases TPR, and ultimately BP (Thijseen et al., 2011)

The activity of these local vasodilatory substances is primarily counterbalanced by vasoconstrictor ET-1. ET-1 is produced in response to chemical (e.g. angiotensin II, catecholamines) or mechanical (shear stress) stimulation of the endothelium (Touyz & Shiffrin, 2003). When bound to ET_A receptors, ET-1 induces vasoconstriction resulting in increases in TPR and BP. However, when bound to ET_B receptors, it triggers the release of NO and elicits vasodilation and has the opposite effect on BP (Pollock et al., 1995).

1.2.2 Effect of Sex on Blood Pressure Regulation

Sex influences the activity of the previously described BP regulation mechanisms and consequently the prevalence of HTN in these populations. Pre-menopausal women consistently have lower arterial BP values in comparison to age-matched men (Dubey et al., 2002). However, this relationship begins to reverse as women enter peri-menopause, which is characterized by a progressive decline in endogenous estrogen production and which ultimately leads to cessation of menstruation known as menopause (Maas & Franke, 2009). Consequently, post-menopausal women have a higher prevalence of HTN in comparison to age-matched men (Ashraf et al., 2006).

Estrogen may contribute to observed differences in sex BP profiles by modulating resting levels of SNS activity. Muscle sympathetic nerve activity (MSNA), a common measure of direct sympathetic outflow, is consistently lower in young normotensive women in comparison to age-matched men (Hart et al., 2009). Furthermore, in young men, SNS activity is directly proportionate to vasoconstrictor tone and TPR, a relationship that does not exist in pre-menopausal women. This sex difference in SNS activity was further explored by Hart and colleagues (2011) with respect to β-adrenergic receptor stimulation. Investigators found that in pre-menopausal women, vasodilation as result of β-adrenergic receptor stimulation stifled the vasoconstriction effect of the SNS, a response that was not observed in age-matched men or post-menopausal women. Young men also possess a compensatory mechanism that modulates Q in response to increases or decreases in MSNA and TPR, which is not seen in men older than 40 years (Hart et al., 2011). Whether this relationship exists in women is unclear (Hart et al., 2011). In addition to modulating neural activity, estrogen also affects local BP regulation by increasing the activity of NO synthase, thus increasing vasodilation via nitric oxide production (Ashraf et al., 2006). This contributes to reduced TPR and BP in the presence of estrogen.

Despite the protective activity of estrogen against HTN, women surpass men in the absolute number of deaths due to CVD (Ashraf, 2006). Recent evidence from Ferrario and colleagues (2013), suggests that the hemodynamic and hormonal characteristics of primary HTN differ in men and women, with an HTN diagnosis boding worse consequences for women. Investigators reported higher pulse pressures, lower Q values, and higher vascular resistance for women in comparison to men for equivalent BP elevations (Ferrario et al., 2013). These findings support the importance of early HTN

intervention for women as well as the need to consider sex differences when prescribing anti-hypertensive therapy.

1.2.3 Blood Pressure Measurement

The most accurate measure of resting BP is directly acquired via the insertion of a catheter into the radial artery. A pressure transducer attached to the catheter provides measures of beat-to-beat systolic BP, diastolic BP and mean arterial BP (MAP; [systolic BP+2(diastolic BP)] / 3) (Parati et al., 1989). However, this procedure requires specialized training, and is invasive and costly. Therefore, more practical techniques are utilized within clinical settings (Parati et al., 1989). Two of the most commonly employed techniques in clinical practice include: auscultatory sphygmomanometry and oscillometry, both of which are measured at the level of the brachial artery (Pickering et al., 2005). The brachial artery is commonly utilized due to its proximity to the heart; systolic BP increases while diastolic BP decreases when measured in more distal arteries (Pickering, 2005). A form of oscillometry known as ambulatory BP monitoring has garnered interest in the clinical community, as evidence suggests it is a better prognostic indicator of CVD, particularly in older women (Sherwood et al., 2012).

Auscultatory Sphygmomanometry

Auscultatory sphygmomanometry is a method of BP measurement that utilizes a cuff and sphygmomanometer to detect Korotkoff sounds (Beevers et al., 2001). The cuff is fitted around an individual's upper arm above the brachial artery, where the ideal cuff size has a bladder length and width that is 80% and 40% of arm circumference respectively (Pickering, 2005). The sphygmomanometer is then placed beneath the cuff followed by cuff inflation. The cuff is then inflated to a level above systolic BP to

occlude arterial blood flow (Beevers et al., 2001). The pressure in the cuff is gradually decreased as the observer listens for Korotkoff sounds which are produced by turbulence in blood flow as arterial BP exceeds that of the cuff (Beevers et al., 2001). The cuff pressure recorded as the first Korotkoff sounds become audible is the individual's systolic BP while the pressure recorded at the end of the sounds represents diastolic BP (Beevers et al., 2001). Although this method is convenient it does not measure arterial pressure directly (Sechrest, 2005). In addition, it relies largely on the skills of the individual recording BP at identifying the onset and offset of Korotkoff sounds (Sechrest, 2005). This is further confounded by age-related hearing loss in practitioners (Pickering, 2005). Cuff size may also bias BP measurements as larger cuffs require more pressure to cause occlusion (Sechrest, 2005). Collectively, these limitations can lead to the misdiagnosis or failure to diagnosis HTN (Pickering, 2005).

Oscillometry

Oscillometry also uses cuff inflation to measure BP however, unlike auscultatory sphygmomanometry, this technique employs a microprocessor to detect oscillatory signals (Shahriari et al., 2003). Following occlusion of the brachial artery, gradual reductions in cuff pressure produce oscillatory signals from which the microprocessor estimates MAP (Shahriari et al., 2003). Using various algorithms and MAP, the microprocessor derives values for systolic and diastolic BP (Shahriari et al., 2003). Automated BP measurement employing oscillometry is the preferred technique for HTN diagnosis over non-automated BP measurement (Leung et al., 2016; Myers et al., 2015) Prominent limitations of oscillometry include underestimation of BP in comparison to catheterization due to the indirect measure of cuff pressure (Bur et al., 2000). In addition, the algorithms used to estimate MAP vary between devices and are often not divulged by

the manufacturer (Pickering, 2005). Although the algorithms utilized to estimate MAP are constantly improving in accuracy and calibration of equipment ensures reliability of measures, clinical diagnosis of HTN remains unacceptably low (Chow et al., 2013).

Ambulatory Blood Pressure

Ambulatory BP monitoring involves the placement of a cuff around the upper arm for assessment of BP at the brachial artery using oscillometry as described above. The cuff is attached to a monitor via an inflationary hose and is programmed to inflate at set time intervals throughout the prescribed measurement period (e.g. 24 hours) (O'Brien et al., 2001). Generally, the ambulatory monitor is programmed to measure BP every 30 minutes during daytime (6am-10pm) and every hour during nighttime (Pickering et al., 2006). These measures are recorded on the monitor and used to generate mean daytime, nighttime and 24 hour BP which can be uploaded to a computer for review (Pickering et al., 2006; O'Brien et al., 2003).

Ambulatory BP measurement offers unique benefits due to its transportability as it provides insight into BP values outside a clinical setting, which often biases measurement through the white-coat effect. This phenomenon accounts for increases in BP as a result of anxiety produced by the clinical setting and is especially prominent in the elderly patient population (Pinto, 2007; Pickering, 2005). White-coat HTN confounds accurate BP measurement and increases the rate of misdiagnosis in this population. Ambulatory BP also provides a better representation of the variability of BP over time as opposed to a specific point in time and consequently greater insight into the efficacy of anti-hypertensive medications (Warren et al., 2010; O'Brien et al., 2001). Furthermore, ambulatory BP monitoring provides the benefit of measuring BP during sleep. Evidence supports nocturnal values of BP as the most sensitive predictors of CVD risk (Boggia et

al., 2011). Individuals who do not experience a 10% or more drop in systolic or diastolic BP during sleep are classified as non-dippers (Leung et al., 2016). Non-dippers are at an increased risk for CVD related morbidity and mortality and therefore dipping status should be assessed when considering the implementation of anti-hypertensive therapy (Leung et al., 2016). In a meta-analysis of hypertensive patients, Fagard (2009) described four dipping categories when examining the ratio of daytime to nighttime ambulatory BP. Mortality was lowest in extreme dippers (ratio ≤ 0.8) when compared to dippers ($0.8 <$ ratio ≤ 0.9) and non-dippers ($0.9 <$ ratio ≤ 1.0), whereas the incidence of cardiovascular events was highest in reverse dippers (ratio > 1.0) (Fagard, 2009). It is important to recall ambulatory BP monitoring employs oscillometry, therefore the algorithms utilized and thus accuracy of BP measurement may vary between devices (Pickering et al., 2005). Furthermore, ambulatory BP values may be imprecise if an individual does not remain still with their cuffed arm at their side during measurement, or if the patient improperly outfits the cuff after having removed it (i.e. to shower) (Pickering et al., 2005).

1.2.4 Pathophysiology of Hypertension

As noted above (Section 1.2 Hypertension), HTN is one of the leading modifiable risk factors for CVD. In spite of this fact, of the approximately 17 million CVD related deaths per year, 9.4 million are attributed to primary HTN (WHO, 2013). Although the direct cause of primary HTN has yet to be identified, elevated BP results from elevations in Q and/or TPR (Khan et al., 2007). The specific mechanism(s) responsible for these changes is unknown, but are likely related to the neural, hormonal or local pathways that regulate BP (Section 1.2.1 Regulation of Blood Pressure).

Numerous studies have linked the development of primary HTN to SNS over-activity (Singh et al., 2010). Uncharacteristically high levels of SNS activity may contribute to HTN development through stimulatory effects on the heart, vasculature and kidneys, producing effects such as increases in Q, TPR and fluid retention (DiBona, 2004). Research also supports dysfunction at the hormonal level of regulation as a contributory factor to HTN development. With respect to the RAAS, high levels of circulating renin can lead to increased angiotensin II and aldosterone production. These abnormal hormone levels cause increased TPR and fluid retention, thereby increasing BP (Singh et al., 2010). Similarly, HTN is associated with endothelial dysfunction which disrupts the production of substances that exert local effects on BP. Specifically, the reduction in bioavailability of NO related to HTN impairs the ability of the vasculature to dilate properly, increasing TPR and subsequently BP (Panza et al., 1990). This impairment of vasodilation is augmented by the increased presence of vasoconstriction factor ET-1 in hypertensive individuals (Schiffrin, 2012).

Genetic, environmental and psychosocial factors also contribute to HTN pathophysiology. Behavioural factors known to influence HTN development include obesity, insulin resistance, excess sodium intake, excess alcohol consumption, physical inactivity, stress, low potassium intake and low calcium intake (Beevers et al., 2001). Furthermore, the presence of psychological symptoms associated with anxiety and depression have been found to promote HTN development. Jonas and colleagues (1997) followed a cohort of normotensive men and women for 7-16 years and found that for individuals 45-64 years old, high scores on measures of anxiety or depression were independent predictors of incident HTN. These findings were mirrored in a study of middle aged women, which observed that increased levels of anxiety and anger as well as

decreased social support increased the likelihood of HTN development for women in midlife (Raikkonen et al., 2001). Psychological traits can also be predictive of long-term HTN development. Yan and colleagues (2003) followed 3308 adults aged 18-30 years and observed that high scores on measures of impatience and hostility were significantly and independently associated with the risk of HTN development at the 15 year follow-up. These environmental and psychosocial factors in concert with gene variants that influence BP regulation have a significant impact on the development of HTN (Singh, 2010).

Concernedly, the prevalence of HTN also increases with age. An individual's risk of developing HTN increases with aging due to structural changes in the arteries, the most prominent of which is large arterial stiffness associated with calcification (Pinto, 2007). HTN development is further promoted during the human aging process due to ramifications such as decreased baroreceptor sensitivity. Arterial stiffness decreases the responsiveness of baroreceptors to conformational changes in the arteries (Weber et al., 1989). Therefore these receptors are not able to relay the necessary information to produce neural-mediated BP reductions (Weber et al., 1989). Furthermore, increased responsiveness to SNS stimuli with age can produce over-activation of the SNS, and thus increased stimulation of the heart and vasculature causing increases in Q and TPR respectively (Weber et al., 1989). The Framingham Heart Study (2002) followed its participants for 30 years and found a continuous increase in systolic BP between the ages of 30-84 years. Notably, Vasan and colleagues (2002) suggest that the residual lifetime risk for HTN in middle-aged and elderly individuals is 90%. Therefore, HTN development becomes a more significant health concern with advancing age, with the incidence of HTN projected to increase due to a larger proportion of the global population

living longer. Taken together, these trends necessitate pragmatic treatment options for this population (WHO, 2013).

1.2.5 Prevention and Treatment of Hypertension

The goal of HTN management is to lower elevated BP to within clinical target ranges. The recommendation for hypertensive individuals is to lower resting systolic BP to $\leq$ 140 mmHg and diastolic BP to $\leq$ 90 mmHg (Leung et al., 2016). For prehypertensive individuals the recommendation is to lower systolic BP to $\leq$ 120 mmHg and diastolic BP to $\leq$ 80 mmHg (Leung et al., 2016). However, a recent large-scale study conducted by the SPRINT research group (2016) in hypertensive individuals over 50 years of age suggests that treatment should aim to reduce systolic BP $\leq$ 120 mmHg as opposed to the standard goal of $\leq$ 140 mmHg in order to significantly reduce cardiovascular event risk (Cushman et al., 2016). Although less definitive, it is recommended to lower 24 hour ambulatory BP to $\leq$ 130/80 mmHg, and daytime ambulatory BP to $\leq$ 135/85 mmHg (Leung et al., 2016).

Current HTN prevention strategies fall under two broad categories: lifestyle modification and pharmacotherapy. Cornerstone lifestyle modifications include: stress reduction, limiting alcohol consumption, healthy dietary habits and regular aerobic physical activity (Khan et al., 2007). Regarding alcohol consumption, it is recommended that hypertensive and normotensive individuals should limit alcohol consumption to $\leq$ 2 drinks per day and not exceed 14 standard drinks weekly for men and 9 drinks weekly for women (Dasgupta et al., 2014). Dietary changes in order to manage HTN are summarized in the DASH (Dietary Approach to Stop Hypertension) diet which recommends increased fruit and vegetable intake as well as reductions in dairy fat, saturated fat and sodium intake (Blumenthal et al., 2010). Regular aerobic physical activity with resistance training

as an adjunct is an integral component of HTN management and will be discussed in further detail below (Section 1.2.6 Exercise Training).

Pharmacotherapy involves the use of medication to decrease BP to within target ranges, and is typically utilized when lifestyle modifications alone are insufficient, or in the presence of secondary HTN (Chobanian et al., 2003). Common medications utilized include calcium channel blockers, which decrease TPR and lower BP; angiotensin enzyme inhibitors, which prevent the formation of the vasoconstrictor angiotensin, subsequently decreasing TPR and BP; diuretics, which result in larger excrements of urine thus combatting fluid retention and subsequently decreasing SV and BP; and β-blockers which prevent E from increasing HR and BP (Chobanian et al., 2003).

Unfortunately, only half of Canadians over 12 years of age are meeting daily fruit and vegetable intake requirements (Statistics Canada, 2012) and only 15% of adults meet current exercise guidelines (Statistics Canada, 2014). Common barriers to exercise include lack of time, unspecific instruction from health care providers, physical discomfort, and inaccessible exercise environments (Schutzer et al., 2004). Similarly, of Canadians diagnosed with HTN and treated pharmacologically, many are not successfully treated to within target ranges (Statistics Canada, 2014). Furthermore, adherence to lifestyle modifications and/or medication may be difficult for certain patient populations such as the elderly due to lack of support, physical limitations, lack of functional independence, and/or adverse side effects of pharmacological treatment (Pinto, 2007; Schutzer et al., 2004). These findings assert that current HTN interventions do not work for everyone and thus novel interventions that can be maintained over the long term must be explored.

1.2.6 Exercise Training

The integral role of physical activity in HTN management is supported by numerous studies which provide evidence for exercise-induced BP reductions (Pescatello et al., 2004; Kelley et al., 2001). The most recent physical activity guidelines from the American College of Sports Medicine (ACSM) regarding HTN management recommend 30-60 minutes of moderate intensity (40 to 60% of an individual's HR reserve), aerobic exercise (e.g. walking, biking, cycling) on most, if not all days of the week (Pescatello et al., 2015). Similarly, the 2016 Canadian Hypertension Education Program prescribes 30-60 minutes of moderate intensity dynamic exercise (e.g. walking, cycling, swimming) 4-7 days per week in addition to routine activities of daily living (Leung et al., 2016). In addition to aerobic activity, dynamic resistance training is recommended as an adjunct 2 to 3 times per week comprising of 8-12 repetitions per exercise targeting all major muscle groups (Pescatello et al., 2015). Until recently, no guidelines or recommendations existed for isometric exercise training, a specialized form of resistance training. In their 2013 Position Statement, the American Heart Association (AHA) endorsed isometric handgrip (IHG) as an alternative method for lowering BP (Brook et al., 2013). Similarly, Hypertension Canada recommends IHG resistance training as an adjuvant to aerobic training (Pescatello et al., 2015). The outlined protocol recommends 2 minute sustained (static) handgrip contractions at 30% of maximum strength, where each contraction is separated by a timed period of rest for a total of 12-15 minutes per session, conducted $\geq$ 3 times per week for 8-12 weeks. The IHG exercise protocol and its effects will be discussed in further detail below (Section 1.3 Isometric Resistance Exercise).

Effects of Acute Aerobic Exercise on Blood Pressure

An acute bout of high-intensity aerobic exercise elicits a linear increase in systolic BP reaching values of ≥ 200 mmHg (MacDonald et al., 2002). An immediate increase in HR due to decreased parasympathetic outflow and increased sympathetic outflow produces 4 to 6 fold increases in Q and subsequently BP (MacDonald et al., 2002). This BP increase is further inflated by vasoconstriction in the venous vasculature in order to increase venous return and SV (MacDonald et al., 2002). Collectively, these responses serve to provide adequate tissue perfusion of working muscles. In order to meet metabolic demands, the arterioles supplying working muscles gradually dilate to promote perfusion, resulting in decreased TPR (MacDonald et al., 2002). This reduction in TPR at the level of the muscle results in overall minimal changes in diastolic BP (slight decrease) during acute aerobic exercise (MacDonald et al, 2002).

Acute aerobic exercise can also cause BP to decrease during the post-exercise period, a phenomenon referred to as post-exercise hypotension (PEH). This effect has been observed for up to 22 hours following bouts of aerobic exercise in both normotensive and hypertensive individuals (Cardoso et al., 2010; Rondon et al., 2002). The magnitude of BP reduction observed is proportional to pre-exercise resting BP in both BP populations, where individuals with the highest baseline values experience the greatest reductions post-exercise (Cardoso et al., 2010; Rondon et al., 2002). Where BP reductions immediately after aerobic exercise have been observed, average reductions in systolic BP and diastolic BP were approximately 8 mmHg and 9 mmHg respectively, in the normotensive population and 10 mmHg and 7 mmHg respectively, in the hypertensive population (MacDonald et al., 2002). The intensity of exercise required to produce PEH is controversial. For example, Pescatello and colleagues (1991) reported no differences in

PEH with exercise intensity varying from 40-75% of maximum oxygen consumption. In contrast Quinn et al (2000), observed greater PEH following high intensity exercise. The mechanisms underlying PEH are unclear however, a sustained inhibition of sympathetic outflow and release of local vasodilatory substances have been implicated (Cardoso et al., 2010; MacDonald et al., 2002). Furthermore, there is a lack of evidence to suggest sex differences in the cardiovascular response to acute aerobic exercise.

Effects of Chronic Aerobic Exercise on Blood Pressure

The body of literature supporting chronic aerobic exercise-induced reductions in resting BP is vast. Overall the evidence suggests that aerobic exercise interventions produce an average BP reduction of approximately 2/2 mmHg and 7/5 mmHg in normotensives and hypertensives respectively (Cornelissen et al., 2013). Collectively, a multitude of studies support the efficacy of aerobic training in reducing resting BP despite the variety of exercise modalities (walking, running, cycling), intensities (30-90% of maximal oxygen reserve), durations (30-60 minutes) and frequencies (1-7 days per week) utilized (Pescatello et al., 2015; Cornelissen et al., 2013; Pescatello et al., 2004; Kelley et al., 2001). Therefore, it is largely suggested that aerobic exercise training-induced BP reductions are minimally influenced by these characteristics of exercise (Pescatello et al., 2004).

The mechanisms responsible for BP reductions following chronic aerobic exercise remain unclear, although due to the multifactorial nature of HTN etiology, several pathways (e.g. neural, hormonal, local) are likely involved. It is currently believed that BP reductions due to aerobic training are more likely related to changes in TPR as chronic aerobic training does not typically induce changes in Q (Cardoso et al., 2010; Pescatello et al., 2005). Furthermore, chronic aerobic training mediated reductions in SNS

activity may attenuate vasoconstriction, subsequently decreasing TPR and BP (Pescatello et al., 2005). Local mechanisms that may play a role in aerobic training-induced BP reductions include increased bioavailability of the vasodilator NO and reduction in circulating ET-1 constriction factor, resulting in decreased TPR and BP (Pescatello et al., 2004; Maeda et al., 2001). In addition, genetic variation may influence the extent of BP reduction by influencing expression of components of the RAAS system. For example, based on their DNA sequence for the angiotensinogen gene certain individuals produce elevated levels of this pro-hormone, resulting in increased TPR. This genotype has also been associated with a blunted BP response to submaximal aerobic exercise (Rice et al., 2002; Rankinen & Bouchard, 2002).

The effect of aerobic training on ambulatory BP is under-investigated, however increasing evidence suggests that aerobic training can also reduce ambulatory BP in normotensive and hypertensive individuals (Cornelissen et al., 2013). Current evidence suggests that aerobic interventions produce average reductions in daytime ambulatory BP of approximately 3/3 mmHg and 3-12/3-7 mmHg for normotensives and hypertensives respectively (Cornelissen et al., 2013). Like resting BP, the mechanism(s) for these training-induced BP reductions is unclear and may mirror the neural and local pathways implicated for resting BP reductions. Additionally, there is a lack of concrete evidence to suggest the sexes differ in resting or ambulatory BP and HR responses to chronic aerobic exercise.

Effects of Acute Dynamic Resistance Exercise on Blood Pressure

An acute bout of dynamic resistance exercise, which involves a series of high-intensity lifts utilizing large muscle groups, produces an immediate increase in both systolic BP and diastolic BP up to 400 mmHg and 200 mmHg respectively (MacDougall

et al., 1985). The magnitude of increase is attributed to the high intramuscular pressure created by compression of the vasculature that is characteristic of resistance exercises (Mayo et al., 1999). This mechanical compression drastically increases TPR and occludes blood flow to working muscles (Mayo et al., 1999). In order to restore blood supply to these tissues, SNS activity increases, thereby increasing both HR and BP in an attempt to restore perfusion (Mayo et al., 1999). The magnitude of the hypertensive response to acute dynamic resistance training is directly proportional to the intensity of contraction by the working muscle and the amount of muscle mass activated (Mayo et al., 1999).

Some evidence exists to suggest PEH occurs following a bout of dynamic resistance exercise (Casonatto et al., 2016; Pescatello et al., 2004). A recent meta-analysis revealed that a single bout of dynamic resistance exercise reduces both resting systolic and diastolic BP by 3 mmHg at 1 hour and 5 mmHg at 90 minutes following the exercise bout (Casonatto et al., 2016). Hypertensive individuals experienced greater reductions in resting systolic and diastolic BP of 9 mmHg and 5 mmHg respectively, in comparison to their normotensive counterparts (Casonatto et al., 2016). Exercise intensity appears to influence the degree of PEH with greater reductions in systolic BP following a high intensity resistance exercise bout (8 mmHg reduction; 80% of 1 repetition max) in contrast to a low intensity bout (6 mmHg reduction; 40% of 1 repetition max) (Rezk et al., 2006). Furthermore, recovery in a supine position and the use of larger muscle groups appears to produce a greater PEH response (Casonatto et al., 2016). The incidence, duration and magnitude of PEH reported are inconsistent and are likely the result of prolonged reperfusion of worked muscles (Casonatto et al., 2016; Cardoso et al., 2010).

The effect of acute dynamic resistance exercise on ambulatory BP is also under-investigated (Cardoso et al., 2010). A study conducted by Sher and colleagues (2011)

investigated the effect of varying volumes of acute resistance exercise on PEH in a population of medicated hypertensives. They found that only the highest volume exercise (40 minutes, 10 exercises, 1 circuit, 20 repetitions, 40% 1 repetition max) produced a reduction in ambulatory systolic BP. In contrast, O'Connor and colleagues (1993) examined the effects of 30 minutes of resistance exercise on ambulatory BP 2 hours post-exercise in young women and found no PEH response. Furthermore, there is a lack of evidence to suggest whether sexes differ in their responses to acute dynamic resistance exercise.

Effects of Chronic Dynamic Resistance Exercise on Blood Pressure

The body of evidence encompassing the training effects of resistance exercise on resting BP is not nearly as extensive as with aerobic training (Cardoso et al., 2010). Meta-analyses of dynamic training in both hypertensive and normotensive populations showed average reductions in systolic BP and diastolic BP of 3 mmHg and 4 mmHg respectively (Cornelissen & Fagard, 2005). Additionally, the overall response of the cardiovascular system to resistance training appears similar in men and women (O'Toole, 1989). Although the reductions are smaller than those experienced with aerobic training it is important to recognize that reductions as small as 2 mmHg in systolic BP reduces stroke and ischemic heart disease related mortality by 10% and 7% respectively (Lewington et al., 2002). As such, dynamic resistance training is recommended by the ACSM as a beneficial adjuvant component of a HTN management fitness regimen (Pescatello et al., 2015). With respect to ambulatory BP, the effect of dynamic resistance training is under-investigated. Of the studies conducted, both reported no significant change in ambulatory BP post-training however further investigation is required (Blumenthal et al., 1991; Van Hoof et al., 1989).

1.3 Isometric Resistance Exercise

1.3.1 Introduction

A novel intervention in the field of HTN management is IHG training, which employs multiple, timed, sustained muscular contractions on a programmed handgrip dynamometer at a set percentage of the maximum voluntary contraction (MVC), during which muscle length and joint angle do not change (Mark et al., 1985). Recently endorsed by the AHA and Hypertension Canada as an alternative treatment to lower BP, this modality is easy to use, time efficient and effective (Carlson et al., 2016; Inder et al., 2016; Leung et al., 2016; Carlson et al., 2014; Millar et al., 2014; Brook et al., 2013). Another form of novel isometric exercise known as isometric leg (IL) exercise appears to elicit similar BP-lowering benefits. Individuals sit in an upright position with a 90 degree flexion of the hip from which position multiple, timed leg extensions are performed at a set percentage of MVC (Inder et al., 2016; Brook et al., 2013; Baross et al., 2012; Devereux et al., 2010). The weight of the evidence suggests that isometric resistance training lowers resting BP in individuals with and without HTN, and can be used effectively as an adjunct to pharmacotherapy and/or traditional exercise programs (Carlson et al., 2016; Inder et al., 2016; Carlson et al., 2014). With respect to the latter, it also provides a treatment option for individuals who are incapable of performing standard aerobic or dynamic resistance exercises (Carlson et al., 2014).

1.3.2 Acute Effects of Isometric Handgrip Exercise on Blood Pressure

Squeezing the handgrip causes an isometric muscle contraction which compresses the underlying vasculature and occludes blood flow (Smith et al., 2005). The lack of blood flow results in a local accumulation of metabolites such as lactic acid, potassium,

hydrogen ions and adenosine resulting in activation of the exercise pressor reflex (EPR) (Smith et al., 2005). The EPR sends afferent signals to the CC from the working muscle, resulting in increased SNS activity (Smith et al., 2005). Consequently, transient elevations in HR attempt to increase perfusion of the active muscle (Smith et al., 2005). The resultant increase in BP exceeds the increase needed to meet the metabolic costs of the isometric exercise, and is dependent on both the size of the muscle and duration of contraction (Laughlin, 1999). Increases in MAP ranging from 10 mmHg to 50 mmHg have been reported in response to an acute bout of IHG exercise (Ray and Carrasco, 2000). Carlson and colleagues (2017) observed changes in BP and HR over the course of four, two minute sustained contractions at 30% MVC in normotensive and prehypertensive individuals. Normotensive participants (n = 60; baseline BP = 115 ± 9/69 ± 8 mmHg) experienced peak increases averaging 154 ± 23 mmHg and 92 ± 14 mmHg for systolic and diastolic BP respectively (Carlson et al., 2017). Prehypertensive participants (n = 60; baseline BP = 136 ± 12/77 ± 7 mmHg) experienced peak increases averaging 174 ± 36 mmHg and 98 ± 22 mmHg for systolic and diastolic BP respectively (Carlson et al., 2017). Wiley and colleagues (1992) investigated the effect of a 2 minute IHG contraction at 30% MVC in healthy normotensive individuals (N = 8; age 20-35 years; resting BP 134/87 mmHg) and found mean increases of 17 mmHg and 16 mmHg for systolic and diastolic BP respectively. The relatively large acute changes in diastolic BP observed during a bout of handgrip exercise are unique and not observed during acute bouts of dynamic aerobic exercise (Millar et al., 2014). With respect to changes in HR during an acute bout of handgrip, Carlson and colleagues (2017) observed larger increases in prehypertensive individuals (67 ± 9 to 79 ± 16 beats/minute) in comparison

to normotensives (68 ± 9 to 75 ± 12 beats/minute). Furthermore, men and women appear to respond similarly to the acute IHG stressor (Wiley et al., 1992).

The effect of acute IHG and IL exercise on PEH is under-investigated. A study conducted by Millar and colleagues (2009) observed PEH of systolic BP (3 mmHg) following 4, 2 minute sustained bilateral contractions at 30% MVC in older normotensive individuals (N = 18; age = 70 $\pm$ 5 years). The same protocol also produced PEH in young normotensive individuals (12/11 mmHg) (Araujo et al., 2011). In contrast, PEH was not observed by Bartol and colleagues (2012) in medicated hypertensives (N = 11; resting BP = 114/61 mmHg) within 22 hours following 4, 2 minute sustained bilateral contractions at 30% MVC. The lack of PEH in this population may be attributed to the BP modulating effects of anti-hypertensive medication as well as the lower resting BP of these individuals in comparison to the older normotensives investigated by Millar and colleagues (2009). Further investigation is required to determine the extent of PEH associated with IHG exercise in varying populations and the underlying mechanism(s) responsible.

1.3.3 Chronic Effects of Isometric Handgrip Training on Blood Pressure

Numerous studies provide compelling evidence for IHG training-induced resting BP reductions in a variety of populations (Carlson et al., 2016; Inder et al., 2016; Millar et al., 2014; Carlson et al., 2014). In general, the IHG protocols employed range from 3 to 5 weekly sessions, for 5 to 10 weeks, with contractions of 30-50% MVC lasting 45 seconds to 2 minutes (Carlson et al., 2016; Inder et al., 2016; Millar et al., 2014; Carlson et al., 2014). A recent meta-analysis of 11 randomized control trials (N = 302) conducted with normotensive and hypertensive adults (age $\geq$ 18 years) reported overall mean reductions

in resting systolic and diastolic BP of 5 mmHg and 4 mmHg respectively as well as 3 mmHg reductions in MAP (Inder et al., 2016). Sub-analyses revealed that participants did not significantly differ for reductions in systolic and diastolic BP based on gender, age or BP classification (Inder et al., 2016). A second meta-analysis conducted by Carlson and colleagues (2014) in normotensive and medicated hypertensive individuals (N = 223; age = ≥18) also reported significant IHG training-induced reductions in BP. Hypertensive participants experienced mean reductions of 4 mmHg and 5 mmHg in systolic and diastolic BP respectively, while those with normotension exhibited mean reductions of 7 mmHg and 3 mmHg in systolic and diastolic BP respectively. Evidence suggests that training duration and frequency influence the degree of BP reduction experienced from IHG training (Inder et al., 2016; Badrov et al., 2013b). An investigation on training dosage by Badrov and colleagues (2013b) found that young women (N = 12; age =18-45 years) who trained 3 times per week and/or 5 times per week for 8 weeks (4, 2 minute bilateral contractions at 30% MVC) experienced mean systolic BP reductions of 6 mmHg. Women who trained in the 5 times per week group achieved this 6 mmHg reduction at the 4 week mark of the 8 week training intervention, in comparison to women who trained 3 times per week and achieved a 6 mmHg reduction at the end of the intervention (Badrov et al., 2013b).

Although less investigated, IL exercise appears to elicit similar benefits. Devereux and colleagues (2010) observed mean reductions in both systolic BP and diastolic BP of 5 mmHg and 3 mmHg respectively in a normotensive population (N = 13; age = 20-40 years) following 4 weeks of bilateral leg training conducted 3 times per week. The training protocol involved 4, 2 minute sustained leg extensions at 24% of MVC. Baross and colleagues (2012) investigated the effects of training intensity in healthy middle-aged

men who trained 3 times per week for 8 weeks (4, 2 minute bilateral leg contractions). Men (N =10; age = 55 $\pm$ 5 years) who trained at 14% MVC experienced mean systolic BP reductions of 11 mmHg. Similarly, Wiles and colleagues (2017) assessed the BP-lowering efficacy of a home-based isometric resistance training protocol in healthy normotensive males (N = 28). Participants conducted 4, 2 minute bouts of wall squats 3 times per week for 4 weeks, resulting in reductions in resting systolic and diastolic BP of 4 mmHg and 3 mmHg respectively (Wiles et al., 2017). IL training has yet to be investigated in the hypertensive population and additional research is required to determine its efficacy as a method of HTN management.

The effect of IHG or IL training on ambulatory BP is under-investigated. Research conducted by Stiller-Moldovan et al (2012b), looked at the effect of 4, 2 minute sustained contractions at 30% MVC, 3 times per week for 8 weeks in well controlled, medicated hypertensives (114/60 mmHg). The investigators reported no significant reductions in ambulatory BP however, clinically relevant reductions in mean 24 hour (3 mmHg) and nocturnal systolic BP (4 mmHg) were noted. However, the lack of significant reduction in this sample may have been attributed to the BP lowering effects of anti-hypertensive medication. Somani and colleagues (2017) observed reductions in 24 hour (men: 4 mmHg, women: 4 mmHg), daytime (men: 3 mmHg, women: 4 mmHg), and nighttime (men: 4 mmHg, women: 3 mmHg), ambulatory systolic BP in young normotensives (N = 24) following 10 weeks of IHG training (Somani et al., 2017). Further investigation is warranted to determine whether IHG training attenuates ambulatory BP and whether sexes differ in this response.

Although numerous studies support the hypotensive effects of IHG and IL training, the mechanism(s) responsible remain equivocal. HTN is associated with

dysfunctional vagal HR modulation, increased SNS activity and endothelial dysfunction (Faulx et al., 2003; Singh et al., 1998; Anderson et al., 1989). As such, hypothesized mechanisms of IHG-induced hypotension have included improved modulation of the ANS and improved endothelium dependent vasodilation (Millar et al., 2014). To investigate the effects of IHG training on ANS modulation, Taylor and colleagues (2003) assessed HR and BP variability following 10 weeks of training in hypertensives. Analysis revealed improved vagal activity and a concurrent reduction in sympathetic modulation. Also associated with HTN, endothelial dysfunction is characterized by reduced bioavailability of the local vasodilator NO, which subsequently impairs endothelium-dependent vasodilation (Panza et al., 1990). It has been hypothesized that the EPR activated during isometric muscle contraction associated with IHG exercise may increase NO formation through an increase in shear stress when vasculature is compressed. Elevated NO would increase vasodilation and subsequently reduce TPR and BP. A study conducted by McGowan and colleagues (2006) investigated the effects of bilateral versus unilateral IHG training in medicated hypertensives. Investigators observed that endothelium dependent vasodilation improved locally within only the trained limbs of participants following 8 weeks of IHG training conducted 3 times per week. Therefore, improvements in endothelial function were not systemic and are not likely responsible for IHG training-induced BP reductions in this population. In contrast, while investigating the effects of training dose on IHG training-induced BP reductions in young normotensive women, Badrov and colleagues (2013b) observed that 8 weeks of IHG training conducted either 3 times or 5 times per week improved resistance vessel endothelial function concomitant with IHG training-induced reductions in systolic BP for both groups. Therefore, the mechanism of IHG training-induced hypotension in this

population may be TPR-mediated. In contrast, Hanik and colleagues (2014) observed mean systolic reductions of 3 mmHg in young normotensive individuals concomitant with IHG training-induced reductions in resting Q. Together these findings suggest that the mechanism(s) responsible for IHG induced hypotension are multi-faceted and may vary depending on population characteristics.

Inter-individual differences in response to IHG training exist, with some individuals lacking a hypotensive adaptation to training across populations. While investigating the potential effects of IHG training using an inexpensive spring-loaded device in the older normotensive population (N = 49; age = 66 years), Millar and colleagues (2008) found that post-menopausal women experienced greater post-training reductions in systolic BP comparison to age-matched men, a significant finding considering the under-representation of women in the IHG literature. In contrast, a recent meta-analysis of isometric resistance training in healthy adults (aged $\geq$ 18 years; N = 302) demonstrated that individuals did not differ in the magnitude of BP attenuation based on gender, age or BP classification (Inder et al., 2016). Similarly, Hanik and colleagues (2012) provided evidence that IHG training is equally effective in reducing resting arterial BP in young (aged 18-40 years) normotensive men and women. In addition to the sex difference in IHG training responsiveness observed by Millar and colleagues (2008) in the older normotensive population, researchers also found that individuals with higher pre-training resting BP values experienced greater reductions post-training. Therefore further research is needed to understand individual variations in responsiveness to IHG training, including the identification of responders versus non-responders, to better promote IHG training as an anti-hypertensive therapy.

1.4 Cardiovascular Reactivity

One method of exploring inter-individual differences in response to IHG training involves assessing cardiovascular responses (BP and HR) elicited by the body when presented various psychophysiological stressors. Cardiovascular reactivity refers to the magnitude of change observed in peak BP and HR during exposure to the stressor from baseline or resting measures (Gerin et al., 2000). The cardiovascular reactivity hypothesis proposes that acute BP elevations in response to a stressor with repeated exposure can produce chronic elevations in resting BP overtime and subsequently the development of HTN (Gerin et al., 2000).

Common laboratory stressors used to assess cardiovascular reactivity include the serial subtraction task (SST; psychological stressor), IHG task (IHGT; physiological stressor) and the cold-pressor task (CPT; physiological stressor) (Sherwood, 1997). The SST involves the subtraction of a 2 digit number from a series of 4 digit numbers that are presented for 5 seconds at a time whilst providing responses aloud (Badrov et al., 2013a; Millar et al., 2009). Increased BP in response to the SST is the result of increases in Q via β-adrenergic stimulation and is classified as a myocardial response (Millar et al., 2009). The IHGT involves one, unilateral two minute sustained contraction at 30% MVC on a handgrip dynamometer (Badrov et al., 2013a). As with the SST, an increase in BP due to the IHGT is the result of an increase in Q via β-adrenergic stimulation and therefore, is also a myocardial response (Badrov et al., 2010). The CPT involves immersion of a peripheral limb (hand or foot) into a cold water bath ($4 \pm 1°C$) for 2-10 minutes (Badrov et al., 2013a; Millar et al., 2009). In contrast, cardiovascular reactivity in response to the CPT is mediated through α-adrenergic vasoconstriction and is classified as a vascular

response (Badrov et al., 2010). Therefore, the CPT effectively acts as a control comparison against responses to the SST and IHGT.

Millar and colleagues (2009) investigated whether cardiovascular reactivity to the CPT and SST were associated with IHG training-induced changes in resting BP in older normotensive participants (N = 17; age = 66 $\pm$ 2 years) following 8 weeks of IHG training. Using a retrospective design, investigators observed that systolic BP reactivity to the SST, but not the CPT was predictive of responsiveness to IHG training. This suggests that like the SST, the mechanism producing IHG training mediated attenuations in BP may also be myocardial mediated. Furthermore, the SST may provide a method for identifying individuals that stand to benefit from IHG training in a clinical setting. Similarly, in the first prospective study to date, Badrov et al (2013a), determined systolic BP reactivity to a SST and IHGT, but not the CPT, was predictive of IHG training success in hypertensive individuals (N = 12; age = 51-74 years). This study also provided the first evidence for the attenuation of cardiovascular reactivity in response to the SST and IHGT post-training. Repeated exposure to a stressor that elicits cardiovascular reactivity may produce chronic elevations in BP and subsequently HTN development (Gerin et al., 2000). This attenuation is thought to explain the reduction of HTN risk associated with aerobic exercise training, therefore attenuation of cardiovascular reactivity by IHG training may also reduce the risk of HTN development (Dimsdale et al., 1986). Furthermore like the SST, the IHGT may also be used as a simple tool to identify which individuals will respond favorably to IHG training.

Somani and colleagues (2015) investigated the relationship between cardiovascular reactivity and resting/ambulatory BP in young normotensive individuals (N = 26; age = 25 $\pm$ 6 years). Following 10 weeks of IHG training 3 times per week (4, 2

minute contractions at 30% MVC) significant training-induced reductions in resting systolic BP were significantly correlated with systolic BP reactivity to the IHGT. However, an association was not identified between pre-training SBP reactivity and IHG training-induced reductions in ambulatory BP. This lack of correlation may be attributed to the inherently high variability in BP during a 24 hour period (Somani et al., 2015). The association between cardiovascular reactivity to psychophysiological stressors and ambulatory BP has yet to be investigated in an older population.

1.5 Summary of Background

In summary, HTN is a major prognostic indicator of CVD and the number of CVD related deaths is projected to increase (WHO, 2013). HTN is a specific concern for the elderly population for whom the residual lifetime risk of HTN development is estimated at 90% (Vasan et al., 2002). Furthermore, the incidence of HTN in women increases dramatically following menopause with as many as 1/3 of post-menopausal Canadian women developing HTN (Routledge et al., 2009). As such primary prevention is key, however, current pharmacological and lifestyle interventions for HTN management are not effective for everyone (Statistics Canada, 2014). This necessitates novel HTN prevention tools such as IHG training, which has proven effective in both normotensive and hypertensive populations (Inder et al., 2016; Leung et al., 2016; Carlson et al., 2014; Millar et al., 2014). IHG training responsiveness has shown inter-individual variability including non-responders across populations and greater BP attenuations in individuals with higher pre-training BP. Although IHG-specific data suggests that older women are the most responsive to training, meta-analyses encompassing IHG and IL training trials provides evidence that men aged $\geq$ 45 years

experience greater post-training BP reductions than age-matched women (Inder et al., 2016; Millar et al., 2008).

Cardiovascular reactivity in response to psycho-physiological stressors may provide insight into these differences and shed light on post-menopausal women who are under-represented in the IHG literature and at an increased risk for HTN development (Routledge et al., 2009).

Previous research has shown that the IHGT may be predictive of post-IHG training resting BP reductions in young normotensive and hypertensive individuals, however whether the IHGT is predictive of BP reductions in the older normotensive population is unknown (Somani et al., 2015; Badrov et al., 2013b). Using cardiovascular reactivity to identify older individuals who are at increased risk for HTN development and who will respond favorably to IHG training affords health care providers a simple yet effective means for prescribing IHG training as anti-hypertensive therapy and a primary prevention tool. Furthermore high cardiovascular reactivity to acute stressors may be associated with chronic BP elevations with repeated exposure to stressors and the effect of IHG training on reactivity is under-investigated (Gerin et al., 2000). Lastly, the effect of IHG training on ambulatory BP, a better prognostic indicator of CVD risk especially in post-menopausal women, is unknown in the older normotensive population.

1.6 References

Ackermann, U. (2004). Regulation of arterial blood pressure. *Surgery (Oxford), 22,* 120a-120f.

Anderson, E., Sinkey, C., Lawton, W., & Mark, A. (1989). Elevated sympathetic nerve activity in borderline hypertensive humans. Evidence from direct intraneural recordings. *Hypertension, 14*, 177-183.

Araujo, C.G., Duarte, C.V., Goncalves, A., Medeiros, H.B., Lemos, F.A., & Gouvea, A.L. (2011). Hemodynamic responses to an isometric handgrip training protocol. *Arquivos Brasileiros de Cardiologia*, *97,* 413-419.

Ashraf, M.S., & Vongpatanasin, W. (2006). Estrogen and hypertension. *Current Hypertension Reports, 8,* 368-376.

Badrov, M., Millar, P.J., & McGowan, C.L. (2010). Role of isometric handgrip training in the management of hypertension: Insights from cardiovascular stress reactivity testing. *Critical Reviews in Physical and Rehabilitation Medicine, 22,* 13-38.

Badrov, M., Horton, S., Millar, P.J., & McGowan, C.L. (2013a). Cardiovascular stress reactivity tasks successfully predict the hypotensive response of isometric handgrip training in hypertensives. *Psychophysiology, 50,* 407-414.

Badrov, M., Bartol, C., DiBartolomeo, M., Millar, P., McNevin, N., & McGowan, C. (2013b). Effects of isometric handgrip training dose on resting blood pressure and resistance vessel endothelial function in normotensive women. *European Journal of Applied Physiology, 11*, 2091-2100.

Baross, A., Wiles, J., & Swaine, I. (2012). Effects of intensity of leg isometric training on the vasculature of trained and untrained limbs and resting blood pressure in

middle-aged men. *International Journal of Vascular Medicine,* 964697.

Bartol, C., Kenno, K., & McGowan, C. (2012). Post-exercise hypotension: Effects of acute and chronic isometric handgrip in well-controlled hypertensives. *Critical Reviews in Physical and Rehabilitation Medicine, 24,* 137-145.

Beevers, G., Lip, G., & O'Brien, E. (2001). Blood pressure measurement: Part II—conventional sphygmomanometry: Technique of auscultatory blood pressure measurement. *British Medical Journal, 322,* 1043-1047.

Blumenthal, J.A., Siegel, W.C., & Appelbaum, M. (1991). Failure of exercise to reduce blood pressure in patients with mild hypertension. Results of a randomized controlled trial. *Journal of the American Medical Association, 266,* 2098-2104.

Blumenthal, J.A., Babyak, M.A., Hinderliter, A., Watkins, L.L., Craighead, L., Lin, P.H., et al. (2010). Effects of the DASH diet alone and in combination with exercise and weight loss on blood pressure and cardiovascular biomarkers in men and women with high blood pressure: the ENCORE study. *Archives of Internal Medicine Journal, 170,* 126.

Boggia, J., Thijs, L., Hansen, T.W., Li, Y., Kikuya, M., Bjorklund-Bodegard, K., & Staesseon, J.A. (2011). Ambulatory blood pressure monitoring in 9357 subjects from 11 populations highlights missed opportunities for cardiovascular prevention in women. *Hypertension, 57,* 397-405.

Brodde, O.E., & Michel, M.C. (1999). Adrenergic and muscarinic receptors in the human heart. *Pharmacology, 51,* 651-690.

Brook, R.D., Appel, L.J., Rubenfire, M., Ogedegbe, G., Bisognano, J.D., Elliott, W.J., Fuchs, F.D., Hughes, J.W., Lackland, D.T., Staffileno, B.A., Townsend, R.R., & Rajagopalan, S. (2013). Beyond medications and diet: Alternative approaches to

lowering blood pressure: A scientific statement from the American Heart Association. *Hypertension, 61,* 1360-1383.

Bur, A., Hirschl, M., Herkner, H., Oschatz, E., Kofler, J., Woisetschlager, C., & Laggner, A. (2000). Accuracy of oscillometric blood pressure measurement according to the relation between cuff size and upper-arm circumference in critically ill patients. *Critical Care Medicine, 28,* 371-376.

Cardoso, C.G., Gomides, R., Quireoz, A., Pinto, G., Lobo, F., Tinucci, T., & Forjaz, C. (2010). Acute and chronic effects of aerobic and resistance exercise on ambulatory blood pressure. *Clinic, 65,* 317-325.

Carlson, D.J., Dieberg, G., Hess, N.C., Millar, P.J., Smart, N.A., et al. (2014). Isometric exercise training for blood pressure management: A systematic review and meta-analysis. *Mayo Clinic Proceedings, 89,* 327-334.

Carlson, D.J., Inder, J., Palanisamy, S.K.A., McFarlane, J.R., Dieberg, G., & Smart, N.A. (2016). The efficacy of isometric resistance training utilizing handgrip exercise for blood pressure management. *Medicine (Baltimore), 95,* e5791.

Carlson, D.J., McFarlane, J.R., Dieberg, G., & Smart, N.A. (2017). Rate pressure responses during an acute session of isometric resistance training: A randomized trial. *Journal of Hypertension and Cardiology, 2,* 1-11.

Carretero, O., & Oparil, S. (2000). Essential hypertension part 1: Definition and etiology. *Circulation, 101,* 329-335.

Casonatto, J., Goessler, K.F., Cornelissen, J.R., & Polito, M.D. (2016). The blood pressure-lowering effect of a single bout of resistance exercise: A systematic review and meta-analysis of randomised controlled trials. *European Journal of Preventative Cardiology, 23,* 1700-1714.

Chen, H., Levine, Y.C., Golan, D.E., Michel T., & Lin, A.J. (2008). Atrial natriuretic peptide-initiated cGMP pathways regulate vasodilator-stimulated phosphoprotein phosphorylation and angiogenesis in vascular endothelium. *Journal of Biological Chemistry, 283,* 4439-4447.

Chobanian, A., Bakris, G., Black, H., Cushman, W., Green, L., Izzo, Jr. J., Jones, D., Materson, B., Oparil, S., & Wright, Jr J. (2003). Joint national committee on the prevention, detection, and evaluation, and treatment of high blood pressure. National heart, lung, and blood institute; National high blood pressure education program coordinating committee. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension, 42,* 1206-1252.

Chow, C.K., Teo, K.K., Rangarajan, S., Islam, S., Gupta, R., Avezum, A., & Yusuf, S. (2013). Prevalence, awareness, treatment and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. *Journal of the American Medical Association, 310,* 959-968.

Cornelissen, V.A., & Fagard, R.H. (2005). Effects of endurance training on blood pressure, blood pressure-regulating mechanisms, and cardiovascular risk factors. *Hypertension, 46,* 667-675.

Cornelissen, V.A., & Smart, N.A. (2013). Exercise training for blood pressure: A systematic review and meta-analysis. *Journal of the American Heart Association, 2,* e004473.

Cushman, W.C., Whelton, P.K., Fine, L.J., Wright, J.T., Reboussin, D.M., Johnson, K.C., & Oparil, S. (2016). SPRINT trial results: Latest news in hypertension management. *Hypertension, 67,* 263-265.

Dampney, R.A.L., Coleman, M.J., Fontes, M.A.P., Hirooka, Y., Horiuchi, J., Li, Y.W., et al. (2002). Central mechanisms underlying short- and long-term regulation of the cardiovascular system. *Clinical and Experimental Pharmacology and Physiology, 29,* 261-268.

Dasgupta, K., et al. (2014). The 2014 Canadian hypertension education program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention and treatment of hypertension. *Canadian Journal of Cardiology, 30,* 485-501.

Devereux, G.R., Wiles, J.D., & Swaine, I.L. (2010). Reductions in resting blood pressure after 4 weeks of isometric exercise training. *European Journal of Applied Physiology, 109,* 601-606.

DiBona, G.F. (2004). The sympathetic nervous system and hypertension: Recent developments. *Hypertension, 43,*147-150.

Dimsdale, J.E., Pierce, C., Schoenfeld, D., Brown, A., Zusman, R., & Graham, R. (1986). Suppressed anger and blood pressure: The effects of race, sex, social class, obesity and age. *Psychosomatic Medicine, 48,* 430-436.

Dubey, R., Oparil, S., Imthum, B., Jackson, E. (2002). Sex hormones and hypertension. *Cardiovascular Research, 53,* 688-708.

Fagard, R.H. (2009). Dipping pattern pf nocturnal blood pressure in patients with hypertension. *Expert Review of Cardiovascular Therapy, 7,* 599-605.

Faulx, M., Wright, A., & Hoit, B. (2003). Detection of endothelial dysfunction with brachial artery ultrasound scanning. *American Heart Journal, 145,* 946-951.

Ferrario, C.M., Jessup, J.A., & Smith, R.D. (2013). Hemodynamic and hormonal patterns of untreated essential hypertension in men and women. *Therapeutic*

Advances in Cardiovascular Disease, 7, 293-305.

Furchgott, R.F. (1983). Role of endothelium in responses of vascular smooth muscle. *Circulation Research, 53,* 557-573.

Gerin, W., Pickering, T.G., Glynn, L., Christenfeld, N., Schwartz, A., Carroll, D., & Davidson, K. (2000). An historical context for behavioral models of hypertension. *Journal of Psychosomatic Research, 48,* 369-377.

Haddy, F.J., & Scott, J.B. (1968). Metabolically linked vasoactive chemicals in local regulation of blood flow. *Physiological Reviews, 48,* 688-707.

Haddy, F.J., Vanhoutte, P.M., & Feletou, M. (2006). Role of potassium in regulating blood flow and blood pressure. *American Journal of Phsyiology, 290,* 546-552.

Hall, J.E., Guyton, A.C., & Mizelle, H.L. (1990). Role of the renin-angiotensin system in control of sodium excretion and arterial pressure. *Acta Physioogica Scandinavica, 591,* 48-62.

Hanik, S.E., Badrov, M.B., Stiller-Moldovan, C., DiBartolomeo, M., Millar, P.J., Clarke, D., et al. (2012). Isometric handgrip training induces equal blood pressure reductions in normotensive males and females without influencing heart rate variability. *Canadian Journal of Cardiology, 28,* S118-S119.

Hanik, S.E., Somani, Y.B., Baross, A.W., Swaine, I.L., Milne, K.J., & McGowan, C.L. (2014). The mechanism underlying the hypotensive effect of isometric handgrip training: Is it cardiac output mediated? *Applied Physiology, 39,* S21.

Hart, E., Charkoudian, N., Wallin, G., Curry, T., Eisenach, J., & Joyner, M. (2009). Sex differences in sympathetic neural-hemodynamic balance: Implications for human blood pressure regulation. *Hypertension, 5,* 571-576.

Hart, E., & Charkoudian, N. (2011). Sympathetic neural mechanisms in human blood

pressure regulation. *Current Hypertension Reports, 13,* 237-243.

Henderson, K.K., & Byron, K.L. (2007). Vasopressin-induced vasoconstriction: Two concentration-dependent signaling pathways. *Journal of Applied Physiology, 102,* 1402-1409.

Herd, J.A. (1970). Overall regulation of the circulation. *Annual Review of Physiology, 32,* 289-312.

Hsia, J., Margolis, K., Eaton, C., Wenger, N., Allison, M., Wu, L., et al. (2007). Prehypertension and cardiovascular disease risk in the women's health initiative. *Circulation, 115,* 855-860.

Inder, J.D., Carlson, D.J., Dieberg, G., McFarlane, J.R., Hess, N.C., & Smart, N.A. (2016). Isometric exercise training for blood pressure management: A systematic review and meta-analysis to optimize benefit. *Hypertension Research, 39,* 88-94.

Jonas, B., Franks, P., & Ingram, D. (1997). Are symptoms of anxiety and depression risk factors for hypertension? *Archives of Family Medicine, 6,* 43-49.

Juenger, J., Schellberg, D., Kraemer, S., Haunstetter, A., Zugck, C., Herzog, W., & Haass, M. (2002). Health related quality of life in patients with congestive heart failure: Comparison with other chronic disease and relation to functional variables. *Heart, 87,* 235-241.

Kelley, G.A., Kelley, K.S., & Vu Tran, Z. (2001). Aerobic exercise and resting blood pressure: A meta-analytic review of randomized, controlled trials. *Preventative Cardiology, 4,* 73-80.

Kellogg, D.L., Zhao, J.L., Coey, U., & Green, J.V. (2005). Acetylcholine-induced vasodilation is mediated by nitric oxide and prostaglandins in human skin. *Journal of Applied Physiology, 98,* 629-632.

Khan et al. (2007). The 2007 Canadian hypertension education program recommendations for the management of hypertension: Part 2 – therapy. *Canadian Journal of Cardiology, 23,* 539-550.

Lafranchi, P.A., & Somers, V.K. (2002). Arterial baroreflex function and cardiovascular variability: Interactions and implications. *American Journal of Physiology, 283,* 815-826.

Larsson, H.P. (2010). How is the heart rate regulated in the sinoatrial node? Another piece to the puzzle. *Journal of General Physiology, 136,* 237-241.

Laughlin, H. (1999). Cardiovascular response to exercise. *Advances in Physiology Education, 277,* 244-259.

Leshnower, B.G., Potts, J.T., Garry, M.G., & Mitchell, .JH. (2001). Reflex cardiovascular responses evoked by selective activation of skeletal muscle ergoreceptors. *Journal of Applied Physiology, 90,* 308-316.

Leung et al. (2016). Hypertension Canada's 2016 hypertension education program guidelines for blood pressure measurement, diagnosis, assessment of risk, prevention and treatment of hypertension. *Canadian Journal of Cardiology, 32,* 569-588.

Lewington, S., Clarke, R., Qizilbash, N., Peto, R., & Collins, R. (2002). Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet, 360,* 1903-1913.

Maas, A.H.E.M., & Franke, H.R. (2009). Women's health in menopause with a focus on hypertension. *Netherlands Heart Journal, 17,* 68-72.

MacDonald, J.R. (2002). Potential causes, mechanisms, and implications of post

exercise hypotension. *Journal of Human Hypertension, 16,* 225-236.

MacDougall, J.D., Tuxen, D., Sale, D.G., Moroz, J.R., & Sutton, J.R. (1985). Arterial blood pressure response to heavy resistance exercise. *Journal of Applied Physiology, 58,* 785-790.

Maeda, S., Miyauchi, T., Kakiyama, T., Sugawara, J., Iemitsu, M., Irukayama-Tomobe, Y., & Matsuda, M. (2001). Effects of exercise training of 8 weeks and detraining on plasma levels of endothelin-derived factors, endothelin-1 and nitric oxide in healthy young humans. *Life Sciences, 69,* 1005-1016.

Mannelli, M., Pupilli, C., Lanzilloti, R., Ianni, L., & Serio, M. (1990). Catecholamines and blood pressure regulation. *Hormone Research in Paediatrics, 34,* 156-160.

Mark, C.L., Victor, R.G., Nerhed, C., & Wallin, B.G. (1985). Microneurographic studies of the mechanisms of sympathetic nerve responses to static exercise in humans. *Circulation Research, 57,* 461-469.

Mayo, J.J., & Kravtiz, L. (1999). A review of the acute cardiovascular responses to resistance exercise of healthy young and older adults. *Journal of Strength and Conditioning Research, 13,* 90-96.

McGowan, C.L., Levy, A.S., Millar, P.J., Guzman, J.C., Morillo, C.A., McCartney, N., & MacDonald, M.J. (2006). Acute vascular responses to isometric handgrip exercise and effects of training in persons medicated for hypertension. *American Journal of Phsyiology, 291,* 1797-1802.

Millar, P., Bray, S., MacDonald, M., & McCartney, N. (2008). The hypotensive effect of isometric handgrip training using an inexpensive spring handgrip training device. *Journal of Cardiopulmonary Rehabilitation and Prevention, 28,* 203-207.

Millar, P., MacDonald, M., Bray, S., & McCartney, N. (2009). Cardiovascular reactivity

to psycholophysiological stressors: association with hypotensive effects of isometric handgrip training. *Blood Pressure Monitoring, 14,* 190-195.

Millar, P., McGowan, C., Cornelissen, V., Araujo, C., & Swaine, I. (2014). Evidence for the role of isometric exercise training in reducing blood pressure: Potential mechanisms and future directions. *Sports Medicine, 44,* 345-356.

Myers, M.G., Kaczorowski, J., Paterson, J.M., Dolovich, L., & Tu, K. (2015). Thresholds for diagnosing hypertension based on automated office blood pressure measurements and cardiovascular risk. *Hypertension, 66,* 489-495.

Nguyen, G., Delarue, F., Burckle, C., Bouzhir, L., Giller, T., & Sraer, J.D. (2002). Pivotal role of the renin/prorenin receptor in angiotensis II production and cellular responses to renin. *Journal of Clinical Investigation, 190,* 1417-1427.

O'Brien, E., Beevers, G., & Lip, G.Y.H. (2001). Blood pressure measurement. *British Medical Journal, 322,* 1110-1114.

O'Brien, E. (2003). Ambulatory blood pressure measurement is indispensable to good clinical practice. *Hypertension, 21,* S11-S18.

O'Connor, P.J., Bryant, C.X., Veltri, J.P., & Gebhardt, S.M. (1993). State anxiety and ambulatory blood pressure following resistance exercise in females. *Medicine & Science in Sports and Exercise, 25,* 516-521.

O'Toole, M.L. (1989). Gender differences in the cardiovascular response to exercise. *Cardiovascular Clinics, 19,* 17-33.

Panza, J.A., Quyyumi, A.A., Brush, J.E., & Epstein, S. (1990). Abnormal endothelium-dependent vascular relaxation in patients with essential hypertension. *New England Journal of Medicine, 323,* 22-27.

Parati, G., Casadei, R., Groppelli, A., Di Rienzo, M., & Manci, G. (1989). Comparison of

finger and intra-arterial blood pressure monitoring at rest and during laboratory testing. *Hypertension, 13,* 647-655.

Pescatello, L.S., Fargo, A.E., Leach, C.N., & Scherzer, H.H. (1991). Short-term effect of dynamic exercise on arterial blood pressure. *Circulation, 83,* 1557-1561.

Pescatello, L.S., Franklin, B., Fagard, R., Farquhar, W., Kelley, G.A., & Ray, C.A. (2004). Exercise and hypertension. *Medicine and Science in Sports and Exercise, 36,* 533-553.

Pescatello, L.S. (2005). Exercise and hypertension: Recent advances in exercise prescription. *Current Hypertension Reports, 7,* 281-286.

Pescatello, L.S., MacDonald, H.V., Lamberti, L., & Johnson, B.T. (2015). Exercise for hypertension: A prescription update integrating existing recommendations with emerging research. *Current Hypertension Reports, 17,* 87.

Pickering, T.G., et al. (2005). Recommendations for blood pressure measurement in humans and experimental animals part 1: Blood pressure measurement for humans: A statement for professionals from the subcommittee of professional and public education of the American heart association council on high blood pressure research. *Hypertension, 45,* 142-161.

Pickering, T.G., Shimbo, D., & Haas, D. (2006). Ambulatory blood-pressure monitoring. *New England Journal of Medicine, 354,* 485-501.

Pinto, E. (2007). Blood pressure and ageing. *Postgraduate Medical Journal, 83,* 109-114.

Pollock, D.M., Keith, T.L., & Highsmith, R.F. (1995). Endothelin receptors and calcium signalling. *FASEB Journal, 9,* 1196-1204.

Prabhakar, N.H. (2000). Oxygen sensing by the carotid body chemoreceptors. *Journal of Applied Phsyiology, 88,* 2287-2295.

Quinn, T.J. (2000). Twenty-four hour, ambulatory blood pressure responses following acute exercise: Impact of exercise intensity. *Journal of Human Hypertension, 14,* 547-553.

Raikkonen, K., Matthews, K., & Kuller, L. (2001). Trajectory of psychological risk and incident hypertension in middle-aged women. *Hypertension, 38,* 798-802.

Rankinen, T., & Bouchard, C. (2002). Genetics and blood pressure response to exercise, and its interactions with adiposity. *Preventative Cardiology, 5,* 138-144.

Ray, C.A., & Carrasco, D.I. (2000). Isometric handgrip training reduces arterial pressure at rest without changes in sympathetic nerve activity. *American Journal of Physiology, 279,* 245-249.

Rezk, C.C., Marrache, R.C., Tinucci, T., Mion, D., & Forjaz, C.L. (2006). Post-resistance exercise hypotension, hemodynamics, and heart rate variability: Influence of exercise intensity. *European Journal of Applied Physiology, 98,* 105-112.

Rice, T., Rankinen, T., Chagnon, Y.C., Province, M.A., Perusse, L., Leon, A.S., et al. (2002). Genome-wide association study of blood pressure and hypertension. *Nature Genetics, 41,* 677-687.

Rondon, M.U.B.P., Alves, M.J.N., Braga, A.M.F., Teixeira, O.T.U., Barretto, A.C.P., Krieger, E.M., & Negrao, C.E. (2002). Postexercise blood pressure reduction in elderly hypertensive patients. *Journal of the American College of Cardiology, 39,* 676-682.

Routledge, F., McFetridge-Durdle, J., & Dean, C. (2009). Stress, menopausal status and nocturnal blood pressure dipping patterns among hypertensive women. *Canadian Journal of Cardiology, 25,* 157-163.

Schiffrin, E.L. (2012). Vascular remodeling in hypertension mechanisms and treatment.

Hypertension, 59, 367-374.

Schillaci, G., Pirro, M., & Mannarino, E. (2009). Assessing cardiovascular risk. *Circulation, 119,* 210-212.

Schutzer, K.A., & Graves, B.S. (2004). Barriers and motivations to exercise in older adults. *Preventative Medicine, 39,* 1056-1061.

Sechrest, L. (2005). Validity of measures is no simple matter. *Health Services Research, 40,* 1584-1604.

Shahriari, M., Rotenberg, D., Nielsen, J., Wiinberg, N., & Nielsen, P. (2003). Measurement of arm blood pressure using different oscillometry manometers compared to auscultatory readings. *Blood Pressure, 12,* 155-159.

Sher, L., Ferriolli, E., Moriguti, J., & Lima, N. (2011). The effect of different volumes of acute resistance exercise on elderly individuals with treated hypertension. *Strength and Conditioning Research, 25,* 1016-1023.

Sherwood, A., Bower, J.K., Routledge, F.S., Blumenthal, J.A., McFetridge-Durdle, J.A., Newby, L.K., & Hinderliter, A.L. (2012). Nighttime blood pressure dipping in postmenopausal women with coronary heart disease. *American Journal of Hypertension, 25,* 1077-1082.

Sherwood, A., Girdler, S.S., Bragdon, E.E., West, S.G., Brownley, K.A., Hinderliter, A.L., & Light, K.C. (1997). Ten-year stability of cardiovascular responses to laboratory stressors. *Psychophysiology, 34,* 185-191.

Singh, J.P., Larson, M.G., Tsuiji, H., Evans, J.C., O'Donnell, C.J., & Levy, D. (1998). Reduced heart rate variability and new onset hypertension. Insights into pathogenesis of hypertension: The Framingham Heart Study. *Hypertension, 32,* 293-297.

Singh, M., Menssah, G.A., & Bakris, G. (2010). Pathogenesis and clinical physiology of hypertension. *Cardiology Clinics, 28,* 545-559.

Smith, S.C., Collins, A., Ferrari, R., Holmes, D.R., Logstrup, S., Zoghbi, W.A. (2005). Our time: A call to save preventable death from cardiovascular disease. *Journal of the American College of Cardiology, 60,* 2343-2348.

Somani, Y.B. (2015). The effect of a 10 week isometric handgrip training protocol on blood pressure (resting and ambulatory) and cardiovascular reactivity in young, normotensive individuals. *University of Windsor Electronic Theses and Dissertations,* 5285.

Somani, Y.B., Baross, A., Levy, P., Zinszer, K., Milne, K., Swaine, I., & McGowan, C., (2017). Reductions in ambulatory blood pressure in young normotensive men and women after isometric resistance training and its relationship with cardiovascular reactivity. *Blood Pressure Monitoring, 22,* 1-7.

Statistics Canada. (2012). Fruit and vegetable consumption. Retrieved from http://www.statcan.gc.ca/pub/82-625-x/2013001/article/11837-eng.htm

Statistics Canada. (2014). Physical activity of Canadian adults: Accelerometer results from the 2007 to 2009 Canadian Health Measures Survey. Retrieved from http://www.statcan.gc.ca/pub/82-003-x/2011001/article/11396-eng.htm

Statistics Canada. (2014). Blood pressure of Canadian adults, 2009 to 2011. Retrieved from http://www.statcan.gc.ca/pub/82-625-x/2012001/article/11714-eng.htm

Stiller-Moldovan, C., Kenno, K., & McGowan, C.L. (2012b). Effects of isometric handgrip training on blood pressure (resting and 24h ambulatory) and heart rate variability in medicated hypertensive patients. *Blood Pressure Monitoring, 17,* 55-61.

Taylor, A.C., McCartney, N., Kamath, M.V., & Wiley, R.L. (2003). Isometric training lowers resting blood pressure and modulates autonomic control. *Medicine and Science in Sports and Exercise, 35,* 251-256.

Theriault, L., Stonebridge, C., & Browarski, S. (2010) The Canadian heart health strategy: Risk factors and future cost implications. *The Conference Board of Canada*.

Thijssen, D.H., Black, M.A., Pyke, K.E., Padilla, J., Atkinsonm G., Harris, R.A., Parker, B., Widlamsky, M.E., Tschakovsky, M.E., & Green, D.J. (2011). Assessment of flow-mediated dilation in humans: A methodological and physiological guideline. *American Journal of Physiology, 300,* 2-12.

Touyz, R.M, & Schiffrin. (2003). Role of endothelin in human hypertension. *Canadian Journal of Physiology and Pharmacology, 81,* 533-541.

Van Hoof, R., Hespel, P., Fagard, R., Lijnen, P., Staessen, J., & Amery, A. (1989). Effect of endurance training on blood pressure at rest, during exercise and during 24 hours in sedentary men. *American Journal of Cardiology, 63,* 945-949.

Vasan, R.S., Beiser, A., Seshadri, S., Larson, M.G., Kannel, W.B., D'Agostino, R.B., & Levy, D. (2002). Residual lifetime risk for developing hypertension in middle-aged women and men. The Framingham Heart Study. *Journal of the American Medical Association, 287,* 1003-1010.

Victor, R.G., Secher, N.H., Lyson, T., & Mitchell, J.H. (1995). Central command increases muscle sympathetic nerve activity during intense intermittent isometric exercise in humans. *Circulation Research, 76,* 127-131.

Warren, R.E., Marshall, T., Padfield, P.L., & Chrubasik, S. (2010). Variability of office,

24-hour ambulatory, and seld-monitored blood pressure measurements. *British Journal of General Practice, 60,* 675-680.

Webb, R.C. (2003). Smooth muscle contraction and relaxation. *Advances in Physiology Education, 27,* 201-206.

Weber, M.A., Neutel, J.M., & Cheung, D.G. (1989). Hypertension in the aged: A pathophysiologic basis for treatment. *American Journal of Cardiology, 63,* 25-32.

Weber, M.A., et al. (2014). Clinical practice guidelines for the management of hypertension in the community. *The Journal of Clinical Hypertension, 16,* 14-26.

Wiles, J.D., Goldring, N., & Coleman, D. (2017). Home-based isometric training induced reductions resting blood pressure. *European Journal of Applied Physiology, 117,* 83-93.

Wiley, R., Dunn, C., Cox, R., Hueppchen, A., & Scott, M. (1992). Isometric exercise training lowers resting blood pressure. *Medicine and Science in Sports and Exercise, 24,* 749-754.

World Health Organization. (2013) A global brief on hypertension; silent killer, global public health crisis. Retrieved from http://www.who.int/cardiovascular_diseases/publications/global_brief_hypertension/en/index.html.

Yan, L., Liu, K., Matthews, K., Daviglus, M., Ferguson, T., & Kiefe, C. (2003). Psychological factors and risk of hypertension: The coronary artery risk development in young adults study. *Journal of the American Medical Association, 290,* 2138-2148.

Chapter 2

Isometric handgrip training-induced reductions in blood pressure: The influence of age and cardiovascular reactivity as an outcome predictor in normotensive women

2.1 Introduction

Human life expectancy has increased dramatically resulting in a trend of global population aging (WHO, 2013). By 2056, it is estimated that one quarter of the Canadian population will be 65 years and older (Statistics Canada, 2008). For many individuals this increased life expectancy comes at the cost of living longer with one or more chronic diseases such as cardiovascular disease (CVD) (Statistics Canada, 2014). CVD is a broad term that encompasses all disorders of the heart and blood vessels and is the second leading cause of death for Canadian men and women (Statistics Canada, 2014). Fortunately, due to advancements in treatment many individuals who may have died from CVD are now able to live with the disease. Consequently, the persistence of individuals with CVD poses strains on the economy. In Canada, coronary heart disease, stroke and heart disease due to hypertension (HTN) incur $21 billion in expenses to provide medication, hospitalization and disability compensation (Theriault et al., 2010). Individuals living with CVD often miss work due to hospitalization and experience lower productivity than non-afflicted individuals (Theriault et al., 2010). In addition, patients living with CVD experience a significant reduction in their quality of life due to the strain of coping with illness (Juenger et al., 2002). On a global scale, CVD accounted for 17.3 million deaths in 2008 and this number is projected to increase to 23.3 million deaths by the year 2030 (WHO, 2013). Accordingly, the World Health Organization has deemed CVD a global health crisis with emphasis on primary prevention of HTN as the key to slowing its deadly progression (WHO, 2013).

HTN, or chronically sustained elevations in arterial blood pressure (BP), is a strong prognostic indicator of CVD and is a preventable risk factor (Schillaci et al.,

2009). Individuals diagnosed with HTN have resting automated office BP $\geq$ 135/85 mmHg and/or are prescribed anti-hypertensive medications (Leung et al., 2016; Myers et al., 2015; Chobanian et al., 2003). Of the populations largely at risk for HTN, older individuals possess an estimated 90% residual risk for the development of HTN in their lifetime (Vasan et al., 2002). Ambulatory BP, which provides insight into 24 hour BP fluctuations, is a more accurate and superior prognostic indicator of CVD risk in comparison to clinical resting BP measures (Boggia et al., 2011; Pickering et al., 2006; O'Brien et al., 2003), particularly in women (Sherwood et al., 2012; Boggia et al., 2011; Pickering et al., 2006; O'Brien et al., 2003).

Current treatment and prevention interventions for HTN include lifestyle modifications and pharmacotherapy, with physical activity as an integral component of HTN management (Pescatello et al., 2015; Blumenthal et al., 2010; Khan et al., 2007). In spite of the proven benefits of exercise in HTN management, only 15% of Canadians are meeting physical exercise guidelines and prescription of anti-hypertensive medication does not successfully manage HTN for many people (Ritchey et al., 2016; Colley et al., 2011). People experience a variety of barriers to exercise adherence including physical discomfort, lack of time, lack of exercise knowledge, unspecific recommendations by healthcare providers and the existence of comorbid conditions, which potentiate exercise intolerance (Schutzer et al., 2004). This poor adherence and/or lack of responsiveness to traditional treatment necessitates novel and effective anti-hypertensive therapy.

One such intervention is isometric handgrip (IHG) training, a novel form of resistance training recently endorsed by the American Heart Association (AHA) and Hypertension Canada (Leung et al., 2016; Brook et al., 2013). The most studied protocol consists of 4, 2 minute sustained bilateral contractions at 30% of maximum voluntary

contraction (MVC) conducted 3 times per week for 8 weeks (Carlson et al., 2014; Millar et al., 2014). Numerous studies have provided evidence for the BP-lowering effectiveness of IHG training in a variety of populations including: men and women, normotensive and hypertensive individuals, young and old, individuals who exercise regularly versus sedentary, as well as those non-medicated and medicated for HTN (Carlson et al., 2016; Inder et al., 2016; Carlson et al., 2014; Millar et al., 2014). The most recent meta-analysis of randomized controlled isometric resistance training trials cites reductions in resting BP of ~5/4 mmHg following training (Inder et al., 2016).

The effects of IHG training on ambulatory BP are not as widely studied. Stiller-Moldovan and colleagues (2012) investigated the effect of 4, 2 minute sustained contractions at 30% MVC, 3 times per week for 8 weeks in well controlled, medicated hypertensives (resting BP: 114 ± 13/61 ± 12 mmHg). The investigators reported no significant reductions in ambulatory BP however clinically relevant reductions in mean 24 hour (~3 mmHg) and nighttime systolic BP (~4 mmHg) were noted. The lack of significant reduction in this sample may have been attributed to the BP lowering effects of anti-hypertensive medication. Similarly, Somani and colleagues (2017) recruited young, healthy normotensive individuals (N = 24) to handgrip train 3 times per week for 10 weeks; reductions were observed in 24 hour (men: 4 mmHg, women: 4 mmHg), daytime (men: 3 mmHg, women: 4 mmHg) and nighttime (men: 4 mmHg, women: 3 mmHg) ambulatory systolic BP. Considering the evidence supporting ambulatory BP as a superior indicator of CVD risk, further investigation is warranted to determine the efficacy of IHG training in attenuating ambulatory BP in various populations (Sherwood et al., 2012; Boggia et al., 2011; Pickering et al., 2006; O'Brien et al., 2003).

The underlying mechanisms responsible for observed reductions in BP remain equivocal. Evidence suggests that IHG training-induced reductions in resting BP may be the result of improved autonomic modulation, improved endothelium-dependent vasodilation and/or reductions in oxidative stress (Badrov et al., 2016; Millar et al., 2014; Badrov et al., 2013b; Millar et al., 2009; McGowan et al., 2007a; McGowan et al., 2007b; McGowan et al., 2006). It is likely that a variety of mechanisms work together to alter BP and the mechanisms at play may vary per population. Furthermore, responses to IHG training exhibit high inter-individual variability. According to a recent meta-analysis, age, gender and BP classification does not mediate IHG training-induced adaptations in systolic and diastolic BP, while certain individuals do not respond to IHG training (Inder et al., 2016; Millar et al., 2014). In contrast, Millar and colleagues (2008) reported greater reductions in post-menopausal women in comparison to age-matched men. The reason for these inter-individuals differences in responsiveness to IHG training is unclear and warrants further investigation in order to optimize exercise prescription.

One method to probe these inter-individual differences in IHG responsiveness is to assess cardiovascular reactivity in response to controlled psychophysiological stressors (Gerin, 2000). Common laboratory stressors used to assess reactivity include the serial subtraction task (SST; a timed mental arithmetic task) and isometric handgrip task (IHGT; a single unilateral contraction on a handgrip dynamometer) (Badrov et al., 2013a; Millar et al., 2009). High cardiovascular reactivity is associated with cardiovascular risk and attenuation of reactivity has been implicated as a mechanism by which aerobic exercise training attenuates cardiovascular risk (Dimsdale et al., 1986). Furthermore, cardiovascular reactivity varies in magnitude per individual and these individual

differences in reactivity are thought to be stable over time and across stress task conditions (Sherwood et al., 1997).

Previous retrospective work in an older normotensive population by Millar and colleagues (2009) demonstrated that systolic BP reactivity to a SST was predictive of IHG training-induced resting BP reductions. Similarly, in a prospective study of hypertensive individuals, the SST and IHGT were predictive of IHG training responsiveness (Badrov et al., 2013a). This study also observed attenuation of cardiovascular reactivity following training suggesting that management of cardiovascular reactivity may be significant in the prevention of HTN (Badrov et al., 2013a).

In contrast, a prospective study of young normotensive men and women revealed that systolic BP reactivity to the IHGT but not the SST, was predictive of reductions in resting systolic BP following ten weeks of IHG training (Somani, 2015). In this sample, ambulatory BP reductions were not predicted by either reactivity to either stress task and reactivity to the stress tasks was not attenuated by training (Somani et al., 2017; Somani, 2015). The relationship between IHG training, cardiovascular reactivity and ambulatory BP is under-investigated. Better understanding the effect of IHG training on ambulatory BP and inter-individual differences in responsiveness to IHG training will aid in addressing the World Health Organization's call to action to improve the primary prevention of HTN.

2.2 Purpose and Hypotheses

The aim of this prospective study was to determine whether systolic BP reactivity to an SST and IHGT could predict responsiveness of resting BP to IHG training in

younger and older normotensive women, in addition to the novel ambulatory measure. Understanding who responds best and how age may affect IHG training outcomes is critical in optimizing this intervention for the primary prevention of HTN.

Following ten weeks of IHG training, it was hypothesized that both young and older women would experience equal reductions in BP (resting and ambulatory) (Inder et al., 2016; Somani, 2015). Furthermore, it was hypothesized that systolic BP reactivity to both an SST and IHGT would be predictive of the magnitude of BP responsiveness (resting and ambulatory) to IHG training in older women, while only reactivity to the IHGT would be predictive of training responsiveness in younger women (Somani, 2015; Badrov et al., 2013a; Millar et al., 2009). Thus, participants with the greatest systolic BP responsiveness to the stressors were hypothesized to experience the greatest IHG training-induced BP reductions (Badrov et al., 2013a; Millar 2009). In addition to the primary study objective, IHG training was also anticipated to attenuate systolic BP reactivity in older women but not young women (Somani, 2015; Badrov et al. 2013a).

2.3 Methods

Study Participants

Fourteen normotensive, young (n = 7; Age: 22 ± 2 years; Resting BP: 103 ± 4/62 ± 7 mmHg) and older (n = 7; Age: 63 ± 7 years; Resting BP: 110 ± 4/63 ± 9 mmHg) women were recruited from Windsor, ON and enrolled in the study (Appendix A). Please note that data collected in the young cohort is comprised of a small subset of data collected in a young normotensive population for Ms. Yasina Somani's graduate thesis (Somani, 2015; M.H.K Thesis, University of Windsor). Inclusion criteria required individuals to be 18-40 years of age in the young cohort and 50-80 years of age in the

older cohort. Exclusion criteria included the presence of known disorders (e.g. HTN) and/or prescribed pharmacotherapies (e.g. beta-blockers) known to influence neurovascular function with the exception of anti-contraceptive medication, and/or physical limitations that could impair exercise performance. This study was cleared by the University of Windsor Research Ethics Board (REB# 13-106).

Study Design

Eligibility and Familiarization

Visit 1

Individuals who expressed interest in the study met with researchers in the Physical Activity and Cardiovascular Research Laboratory (PACR Lab – HK 240, University of Windsor, Windsor, ON, Canada). Upon arrival, potential participants read a consent form and letter of information explaining the intended research (Appendix B and C). Following explanation of all parts of the study and acquisition of written and informed consent, medical history was obtained via a brief questionnaire (Appendix D). Next, resting BP was measured using standard laboratory protocol following ten minutes of seated rest with a brachial artery oscillometric device (Dinamap Carescape v100, Critikon, Tampa, Florida, USA; Appendix E) to ensure the inclusion criterion of normotension (< 140/90 mmHg) was met. In brief, a cuff was placed around the upper dominant arm and inflated to a pressure greater than systolic BP in order to occlude the brachial artery (Somani, 2015; Badrov et al., 2013a). Four measures were obtained, with two minute rest intervals between each measure. The first measure was discarded and the final three measures averaged to assess eligibility. Lastly, any final questions or concerns

posed by the participant were addressed, and participants were reminded of their right to withdraw from the study at any time without penalty.

Visit 2

At least 24 hours following Visit 1, potential participants returned for a second visit. First, resting BP was measured as previously described (Section Visit 1). If the average resting BP values from Visits 1 and 2 were < 140/90 mmHg participants underwent a familiarization session during which time they were able to experience all techniques employed during the investigation. This served to habituate participants to the testing protocol and thus minimized the effects of anxiety or unfamiliarity on testing variables. Finally, participants completed a physical activity questionnaire (PAR-Q; Appendix F). Participants who answered 'yes' to any of the questions posed, were issued an additional questionnaire (PARmed-X; Appendix G) completed by their health care provider (e.g. physician or nurse practitioner). In addition, all participants received two letters for their health care provider: the first, a notification of the participant's involvement in the study and the second was signed by the health care-provider to acknowledge study participation (Appendix H).

Testing

Upon receipt of the completed health care provider documents to determine final eligibility, baseline testing occurred to assess BP as well as cardiovascular reactivity in response to a SST and IHGT. All testing took place in a quiet, temperature-controlled room (20-25^{o}C) following a 24 hour abstinence from alcohol consumption and vigorous activity, in addition to a 12 hour abstinence from caffeine. All pre-menopausal women were tested during the follicular phase of their menstrual cycle. Baseline testing was

repeated following 10 weeks of IHG training, at least 48 hours after the final training session and at the same time of day (within 2 hours) of their baseline testing time.

To account for potential confounding influences of anxiety on cardiovascular reactivity responses, participants completed a State-Trait Anxiety Inventory (young women) or a Depression Anxiety Stress Scales questionnaire (older women) prior to testing (Appendix I; as the latter has been shown to have high internal consistency and may better differentiate anxiety, depression and stress, it was used in the more recent data collection procedures involving the older women). Resting BP and heart rate (HR) were measured as described previously (Section Visit 1). Participants completed two cardiovascular reactivity tasks in randomized order. During each stress task, BP and HR were collected in minute intervals via brachial artery oscillometry (Dinamap Carescape v100, Critikon, Tampa, Florida, USA; Appendix E). Task order was maintained during post-training testing. In addition, beat-to-beat HR was continuously collected via single-lead electrocardiography (AD instruments, Colorado Springs, Colorado, USA; Appendix J) using a data acquisition system (PowerLab ML 870/P, AD instruments, Colorado Springs, Colorado, USA; Appendix K). HR and BP were monitored for at least ten minutes following each task to ensure stabilization to baseline values.

Serial Subtraction Task

Participants viewed a computer monitor displaying a 4 digit number from which they verbally subtracted 13 at pre-testing and 17 at post-testing. Each of the 25 numbers displayed were visible for 5 seconds during which time the participant provided their response aloud. The number of correct and incorrect responses was recorded (Somani, 2015; Badrov et al., 2013a).

Isometric Handgrip Task

Participants completed a single 2 minute isometric sustained contraction at 30% of their MVC with their non-dominant hand on a programmed handgrip dynamometer (ZonaPLUS, Zona HEALTH, Boise, Idaho, USA; Appendix L). MVC was determined at the onset of the task via linear load cells contained within the IHG device (Somani, 2015; Badrov et al., 2013a**).**

Ambulatory Blood Pressure

At the completion of the laboratory testing session, participants were fitted with a 24 hour ambulatory BP monitor (SpaceLabs 90207 Ambulatory BP Monitor, SpaceLabs Inc., Redmond, Washington, USA; Appendix M). For the following 24 hours, BP was measured and recorded by the monitor every half hour during waking hours (6am-10pm) and every hour during nighttime hours (10pm-6am) (Somani, 2015; Badrov et al., 2013a; Pickering et al., 2006). In order to ensure standardization of diet and activities during pre-training and post-training measures of ambulatory BP, participant diet and activities during the 24 hour period were discussed and recorded (Appendix N) with participants. These behaviours were revisited and encouraged during the post-training measure of ambulatory BP (Somani et al., 2017; Stiller-Moldovan et al., 2012).

Training

All participants trained 3 times per week for 10 weeks using the bilateral IHG exercise protocol, which comprises four, 2-minute sustained contractions performed at 30% of MVC (Somani, 2015; Badrov et al., 2013a). Each contraction was separated by a 1 minute rest period requiring a total of 12 minutes for completion. All training sessions were supervised by an exercise trainer in the PACR Laboratory. Exercise trainers logged

training progress (MVC scores; % compliance; and changes to exercise/medication) in the participant's exercise log (Appendix O). To ensure participant safety and preparedness for isometric exercise, resting BP and HR were measured prior to each training session.

2.4 Statistics

One-way ANOVAs were performed on baseline resting and ambulatory BP measures to examine initial differences between young and older women. A two-way repeated measures ANOVA was used to determine the training effects of IHG exercise in young and older women (independent variables: time and age) on the following dependent variables: resting arterial BP (systolic BP, diastolic BP, mean arterial pressure; MAP), ambulatory BP (mean 24 hour, daytime and nighttime), resting and ambulatory HR as well as pulse pressure (PP; systolic BP - diastolic BP).

To determine cardiovascular reactivity (systolic BP, diastolic BP and HR responses) to the two stress tasks, the difference between peak task values and resting values were calculated (Jennings et al., 1992). The relationship between cardiovascular reactivity to each task and IHG training adaptations was assessed using Pearson correlation coefficients. Residualized change scores in systolic BP were used for the correlation analysis as baseline BP and change in BP post-training have proven correlated effects (Llabre et al., 1991; Millar et al., 2007). Residualized change scores were determined by regressing change in systolic BP following the intervention on pre-intervention systolic BP. The regression analysis was performed for both resting and ambulatory systolic BP.

A two-way repeated measures ANOVA was utilized to determine whether cardiovascular reactivity to the stress tasks was attenuated by IHG training in either the young or older women. All data was analyzed using IBM SPSS Statistics 22 software (SPSS Inc., Chicago, Illinois, USA) and statistical significance was determined at $P \leq 0.05$. All data are presented as mean ± standard deviation (SD) unless otherwise stated. All raw and statistical data are presented in appendices P and Q respectively.

2.5 Results

Participant Baseline Characteristics

All 14 participants enrolled in the study completed 10 weeks (30 sessions) of IHG training. During this time, no changes in exercise, diet, physical activity or prescribed medication were reported. Average compliance to the IHG exercise protocol was 93% for both young and older women, and the average MVC was 52 lbs and 40 lbs respectively. MVC did not change in either group following ten weeks of training ($P > 0.05$). Of the 14 women, only 12 participated in the ambulatory BP measurement portion of the study (n = 7 young women, n = 5 older women). All 14 women completed both stress tasks at baseline testing however only 13 participated in the SST during post-testing (n = 7 young women, n = 6 older women). No adverse events were reported in response to the testing or IHG training protocols.

Younger and older women did not differ significantly at baseline with respect to the following characteristics: height, weight, resting systolic and diastolic BP, resting MAP and PP, resting HR, ambulatory systolic and diastolic BP (24 hour, daytime and nighttime), and ambulatory HR (24 hour, daytime and nighttime) (all $P > 0.05$). Conversely, age and body mass index (BMI) were significantly different between the two

groups ($P < 0.05$). Participant baseline characteristics are summarized in Table 1. Following ten weeks of IHG training, measures of state and trait anxiety remained unchanged in young women while measures of depression, anxiety and stress remained unchanged in older women (all $P > 0.05$).

Table 1. Participant Baseline Characteristics

Characteristics	**Young Women (n = 7)**	**Older Women (n = 7)**
Age (years)	22 ± 1*	63 ± 7
Height (cm)	169 ± 10	162 ± 5
Weight (kg)	62 ± 11	68 ± 14
BMI (kg/m^2)	22 ± 2*	26 ± 4
Resting Systolic BP (mmHg)	103 ± 4	110 ± 13
Resting Diastolic BP (mmHg)	62 ± 7	63 ± 9
Resting HR (beats/minute)	71 ± 10	66 ± 7
Resting MAP (mmHg)	75 ± 5	78 ± 10
Resting PP (mmHg)	41 ± 5	47 ± 7
Baseline Ambulatory Measures†		
24 Hour Systolic BP (mmHg)	120 ± 4	119 ± 15
Daytime Systolic BP (mmHg)	123 ± 5	123 ± 15
Nighttime Systolic BP (mmHg)	115 ± 6	111 ± 14
24 Hour Diastolic BP (mmHg)	70 ± 6	70 ± 8
Daytime Diastolic BP (mmHg)	73 ± 7	72 ± 8
Nighttime Diastolic BP (mmHg)	65 ± 7	63 ± 8
24 Hour HR (beats/minute)	73 ± 10	69 ± 6
Daytime HR (beats/minute)	76 ± 11	71 ± 6
Nighttime HR (beats/minute)	70 ± 10	66 ± 6

BMI, body mass index; BP, blood pressure; HR, Heart Rate; MAP, mean arterial pressure; PP, pulse pressure. Values are mean ± SD; † of the 14 women, 12 completed the ambulatory measurements (young n = 7, older n = 5);*Significantly different from older women ($P < 0.05$). Results comprise of a small subset of data from the young normotensive cohort recruited for Ms. Yasina Somani's graduate thesis (Somani, 2015; M.H.K, University of Windsor).

Effects of IHG Training on BP and HR

Following 10 weeks of IHG training, significant reductions in resting systolic BP were observed in both young (103 ± 4 mmHg to 100 ± 3 mmHg) and older women (110 ± 13 mmHg to 103 ± 10 mmHg; $P < 0.05$, see Figure 1) and no interaction was observed between the two groups over time ($P = 0.37$, partial $\eta^2 = 0.07$). In contrast, resting diastolic BP, HR, MAP and PP remained unchanged in both young and older women following the intervention (all $P > 0.05$, see Table 2).

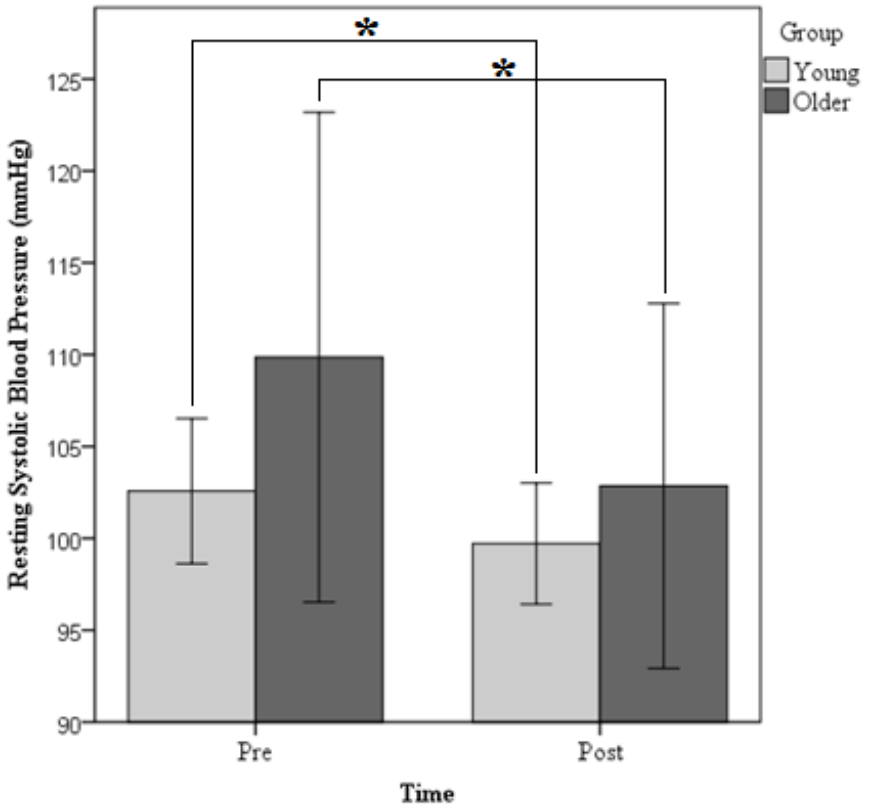


Figure 1. Effect of 10 Weeks of IHG Training on Resting Systolic BP in Young (n = 7) and Older Women (n = 7). Values are mean ± SD, RM ANOVA; *Significantly different from pre-training ($P < 0.05$). Results comprise of a small subset of data from the young normotensive cohort recruited for Ms. Yasina Somani's graduate thesis (Somani, 2015; M.H.K, University of Windsor).

Table 2. Resting Cardiovascular Adaptations to IHG Training

	Young (n = 7)		**Older (n = 7)**	
	Pre	Post	Pre	Post
Resting Diastolic BP (mmHg)	62 ± 7	62 ± 7	63 ± 9	61 ± 3
MAP (mmHg)	75 ± 5	74 ± 5	78 ± 10	74 ± 4
PP (mmHg)	41 ± 5	38 ± 5	47 ± 7	42 ± 10
Resting HR (beats/minute)	71 ± 10	68 ± 12	66 ± 7	69 ± 5

BP, blood pressure; MAP, mean arterial pressure; PP, pulse pressure; HR, heart rate. Values are mean ± SD, RM ANOVA (all $P > 0.05$). Results comprise of a small subset of data from the young normotensive cohort recruited for Ms. Yasina Somani's graduate thesis (Somani, 2015; M.H.K, University of Windsor).

IHG training yielded significant reductions in measures of 24 hour ($P < 0.05$) and daytime ambulatory systolic BP ($P < 0.05$) in both young (120 ± 4 mmHg to 116 ± 5 mmHg) and older women (119 ± 15 mmHg to 112 ± 14 mmHg) (see Figure 2). No interaction was observed between groups over time for measures of 24 hour ambulatory systolic BP ($P = 0.14$, partial $\eta^2 = 0.21$) or daytime ambulatory systolic BP ($P = 0.14$, partial $\eta^2 = 0.21$). No changes were observed in the following ambulatory measures in either group following 10 weeks of IHG training: 24 hour diastolic BP and HR, daytime diastolic BP and HR, nighttime BP and HR (all $P > 0.05$, see Table 3).

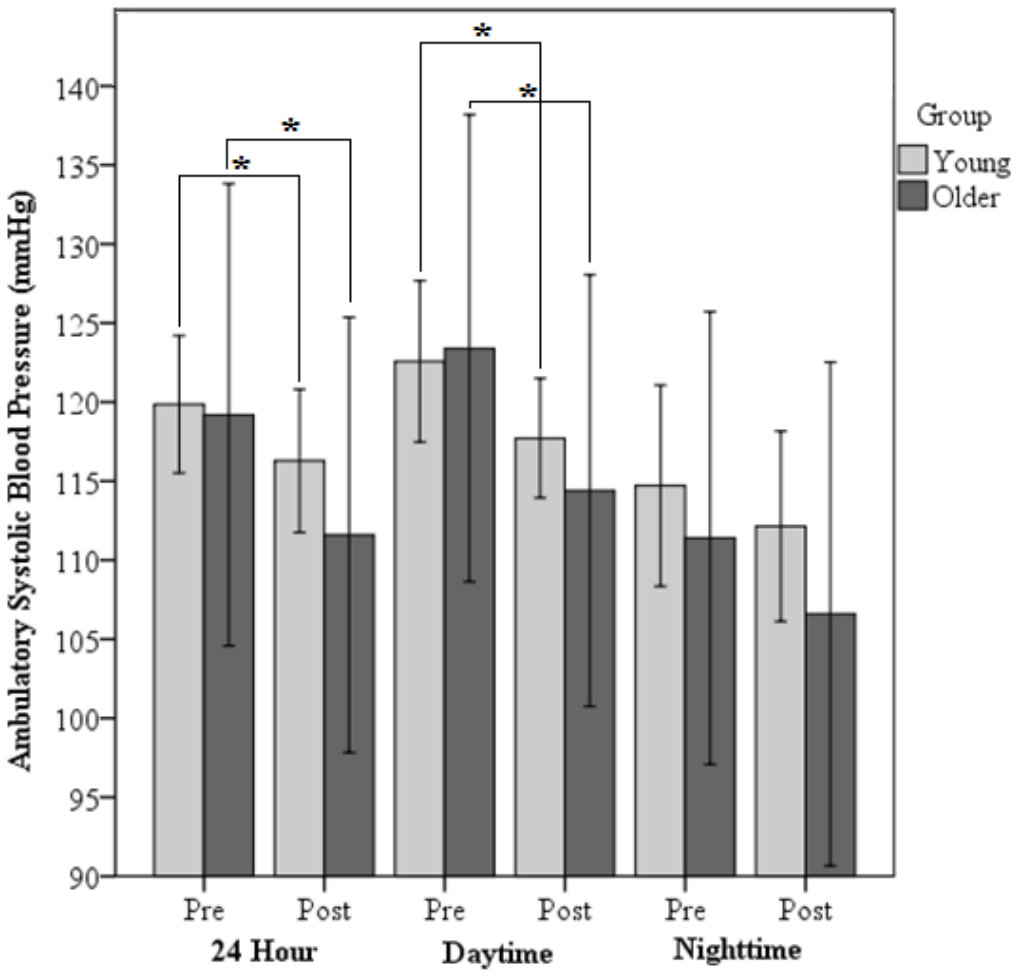


Figure 2. Effects of 10 Weeks of IHG Training on 24 Hour, Daytime and Nighttime Ambulatory Systolic BP in Young (n = 7) and Older (n = 5) Women. Values are mean ± SD, RM ANOVA; * Significantly different from pre ($P < 0.05$). Results comprise of a small subset of data from the young normotensive cohort recruited for Ms. Yasina Somani's graduate thesis (Somani, 2015; M.H.K, University of Windsor).

Table 3. Effects of IHG Training on Ambulatory Diastolic BP and HR

	Young (n = 7)		**Older (n = 5)**	
	Pre	Post	Pre	Post
Ambulatory Diastolic BP (mmHg)				
24 Hour	70±6	68±3	70±8	66±6
Daytime	73±7	70±4	72±8	69±6
Nighttime	65±7	63±5	63±8	60±7
Ambulatory HR (beats/minute)				
24 Hour	73±10	73±12	69±6	72±7
Daytime	76±11	74±11	71±6	74±7
Nighttime	70±10	71±14	66±6	68±8

BP, blood pressure; HR, heart rate. Values are mean ± SD, RM ANOVA (all $P > 0.05$). Results comprise of a small subset of data from the young normotensive cohort recruited for Ms. Yasina Somani's graduate thesis (Somani, 2015; M.H.K, University of Windsor).

Cardiovascular Reactivity as a Predictor of IHG Training Effectiveness

Cardiovascular reactivity to the IHGT and SST at baseline and its relationship to IHG training adaptations in resting BP and HR are displayed in Table 4. Older women had significantly higher systolic BP reactivity to the SST ($P < 0.05$) but not the IHGT ($P > 0.05$) in comparison to the younger cohort. Systolic BP, diastolic BP, and HR reactivity to both the SST and IHGT were not associated with significant adaptations in resting systolic BP in either younger or older women (all $P > 0.05$). Similarly, no association was observed between any measure of cardiovascular reactivity and reduction in daytime ambulatory systolic BP in either group (all $P > 0.05$). Systolic BP reactivity to the IHGT, but not the SST, was associated with significant IHG training-induced reductions in 24 hour ambulatory systolic BP for older women ($P < 0.05$, see Figure 3) however, this relationship was not observed in the younger cohort ($P > 0.05$).

Table 4. Baseline Cardiovascular Reactivity and the Relationship to IHG Training Adaptations in Resting BP and HR

	Δ Systolic BP (mmHg)	***R***	***P***	**Δ Diastolic BP (mmHg)**	***r***	***P***	**Δ HR (beats/ minute)**	***r***	***P***
Young (n = 7)									
SST	10 ± 5*	-0.11	0.81	8 ± 5	0.61	0.15	8 ± 4	-0.06	0.90
IHGT	10 ± 2	-0.14	0.77	9 ± 4	0.72	0.07	8 ± 5	0.56	0.20
Older (n = 7)									
SST	18 ± 9	-0.05	0.91	10 ± 6	0.21	0.65	7 ± 4	-0.45	0.31
IHGT	11 ± 7	0.16	0.74	5 ± 4	0.04	0.93	4 ± 3	-0.64	0.12

BP, blood pressure; HR, heart rate; SST, serial subtraction task; IHGT, isometric handgrip task. Values are mean ± SD; One-way ANOVA;*Significantly different from older women ($P < 0.05$). Results comprise of a small subset of data from the young normotensive cohort recruited for Ms. Yasina Somani's graduate thesis (Somani, 2015; M.H.K, University of Windsor).

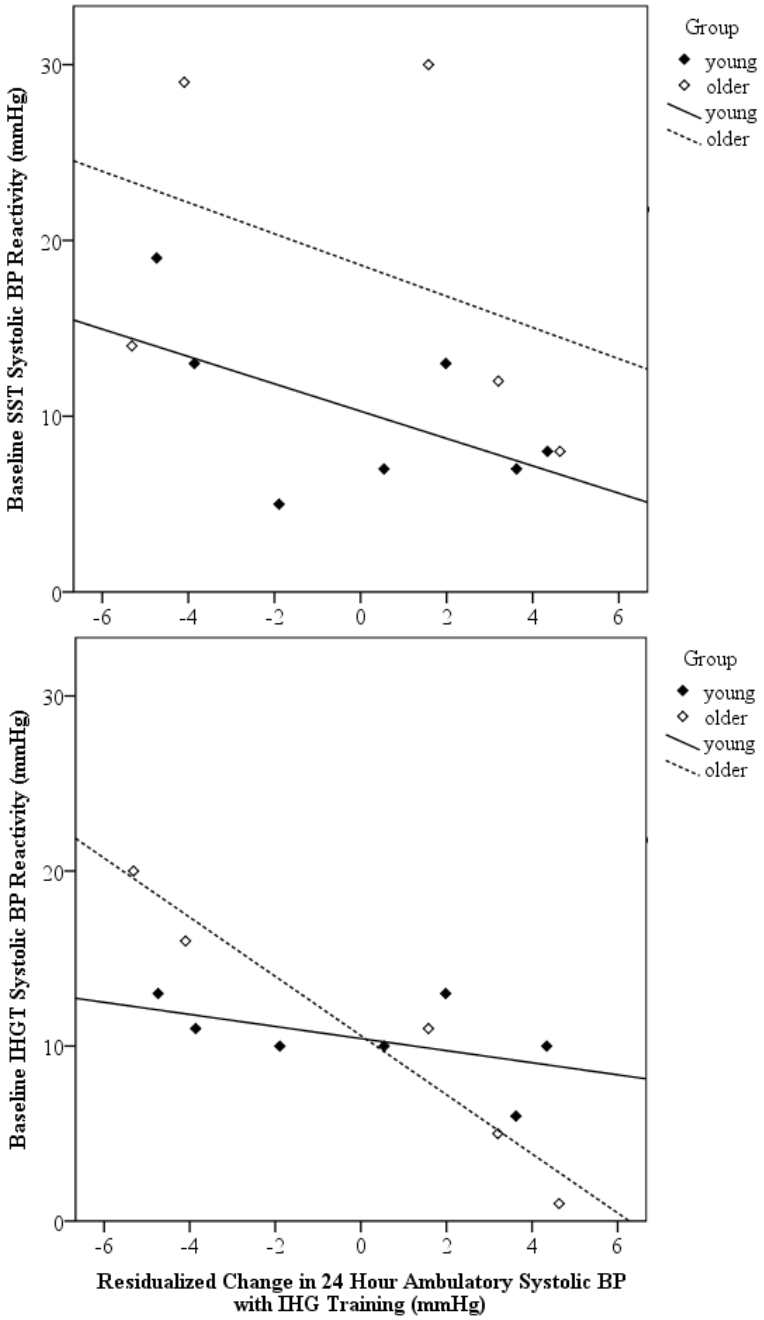


Figure 3. Relationship Between IHG Training-Induced Reductions in Ambulatory Systolic BP and Systolic BP Reactivity to a (i) SST in Young (n = 7; r = -0.57, *P* = 0.19) and Older Women (n = 5; r = -0.39, *P* = 0.52) (ii) IHGT in Young (n = 7; r = -0.52, *P* = 0.23) and Older Women (n = 5; r = -0.97, *P* = 0.01). BP, blood pressure; IHG, isometric handgrip; SST, serial subtraction task; IHGT, isometric handgrip task. Results comprise of a small subset of data from the young normotensive cohort recruited for Ms. Yasina Somani's graduate thesis (Somani, 2015; M.H.K, University of Windsor).

Effect of IHG Training on Cardiovascular Reactivity

Following the 10 week IHG training intervention, all measures of cardiovascular reactivity in response to the SST and IHGT remained unchanged (all $P > 0.05$, see Table 5).

Table 5. Cardiovascular Reactivity Pre- and Post-IHG Training

	Young (n = 7)		**Older (n = 6)**	
	Pre	**Post**	**Pre**	**Post**
IHGT				
Δ Systolic BP (mmHg)	10 ± 5	9 ± 4	18 ± 9	16 ± 5
Δ Diastolic BP (mmHg)	8 ± 5	7 ± 5	10 ± 6	10 ± 5
Δ HR (beats/minute)	8 ± 4	10 ± 3	7 ± 4	6 ± 4
SST				
Δ Systolic BP (mmHg)	10±2	13±3	11±7	13±8
Δ Diastolic BP (mmHg)	9±4	10±5	5±4	5±3
Δ HR (beats/minute)	8±5	11±3	4±3	4±2

BP, blood pressure; HR, heart rate; IHGT, isometric handgrip task; SST, serial subtraction task. Values are mean ± SD; RM ANOVA (all $P > 0.05$). Results comprise of a small subset of data from the young normotensive cohort recruited for Ms. Yasina Somani's graduate thesis (Somani, 2015; M.H.K, University of Windsor).

2.6 Discussion

These study findings add to the growing body of evidence supporting the efficacy of IHG training in attenuating both resting and ambulatory BP, and provides the first direct comparison of the effects of IHG training between young and older women. In accordance with our hypothesis, both young and older women experienced significant reductions in resting systolic BP. These reductions in resting BP were concomitant to significant reductions in measures of 24 hour and daytime systolic ambulatory BP - measures considered to have greater prognostic value than resting BP in identifying CVD risk (Sherwood et al., 2012; Boggia et al., 2011; Pickering et al., 2006; O'Brien et al.,

2003). Furthermore, systolic BP reactivity to an IHGT was associated with reductions in 24 hour ambulatory systolic BP in the older cohort, such that the higher systolic BP rose during the IHGT at baseline, the greater the observed decrease in BP following IHG training. This suggests that systolic BP reactivity to an IHGT may provide a tool for prescribing preventative therapy to older individuals who are at heightened risk for HTN development.

Effects of IHG Training on BP and HR

As hypothesized, both young and older women experienced equal reductions in resting systolic BP, which further supports the efficacy of IHG training as a BP lowering intervention in these populations (Inder et al., 2016; Carlson et al., 2014; Millar et al., 2014). This observation aligns with findings from a recent meta-analysis by Inder and colleagues (2016) that age does not influence IHG training-induced reductions in resting systolic BP.

In contrast to numerous studies assessing the effects of an IHG training intervention in both normotensive and hypertensive participants, no significant reductions in diastolic BP, PP, or MAP were observed in the current study (Inder et al., 2016; Carlson et al., 2014; Millar et al., 2014). Inder and colleagues (2016), reported significant and greater reductions in MAP for individuals $\geq$ 45 years of age in comparison to a younger cohort. The older women in the present study did not experience significant reductions in MAP in comparison to the younger women however, examination of estimates of effect size suggests that with a larger sample significant differences in MAP (partial $\eta^2 = 0.17$) and PP (partial $\eta^2 = 0.28$) may have been observed following ten weeks of IHG training. This discrepancy may be attributed to differences in the baseline BP of

the studied populations as individuals with higher BP tend to experience a more pronounced BP adaptation to IHG training (Inder et al., 2016; Carlson et al., 2014; Millar et al., 2014). In the present investigation, baseline BP values were similar between groups and well below the limit for normal BP classification, which may have contributed to a muted response to the IHG stimulus in this sample. Similarly, the use of a stronger training stimulus in the form of increased percent MVC, increased training frequency or duration of training may be more likely to yield reductions in diastolic BP, PP and MAP whereas the current protocol did not.

Recent meta-analyses have reported slight statistical changes in HR (~1-2 beat/min) following IHG training (Inder et al., 2016; Carlson et al., 2014; Millar et al., 2014). No changes in resting HR were observed following the 10 week training intervention which supports previous findings in normotensive individuals which may have been underpowered to detect training-induced changes in HR (Badrov 2013b; Devereux et al., 2010; Wiles et al., 2010; Millar et al., 2009; Millar et al., 2008). A greater IHG stimulus (larger MVC percentage), training frequency and/or duration may be required to elicit HR adaptations in the healthy normotensive population.

Significant reductions in 24 hour and daytime systolic ambulatory BP were observed in both cohorts following 10 weeks of IHG training, as observed by Somani and colleagues (2017) in young normotensives however, nighttime systolic ambulatory BP remained unchanged. The latter finding is in contrast to our initial hypothesis and likens to the work of Stiller-Moldovan and colleagues (2012) in medicated hypertensives, where clinically relevant reductions in nighttime systolic ambulatory BP were observed following a 10 week IHG intervention. These reductions were deemed clinically significant as evidence suggests that a reduction of 2 mmHg in systolic BP is associated

with reductions in mortality from stroke and heart disease (Verdecchia et al., 2012). Therefore, although not statistically significant, the reductions in nighttime ambulatory systolic BP may be considered clinically significant for both young (n = 4) and older women (n = 3). Examination of estimates of effect size also suggests that with a larger sample size, significant differences in nighttime ambulatory systolic BP (partial $\eta^2 = 0.28$) may have been observed following ten weeks of IHG training. No changes were observed in measures of ambulatory diastolic BP and HR as paralleled by Stiller-Moldovan and colleagues (2012) in the medicated hypertensive population and Somani and colleagues (2017) in the young normotensive population. Due to inherently high variability in BP throughout a 24 hour time period, it may be fruitful to collect ambulatory BP data over a time period longer than 24 hours to better assess the effects of IHG training on ambulatory BP (Warren et al., 2010). Collectively, these findings in addition to the superior reliability of ambulatory BP at indicating CVD risk warrants further research on the effects of IHG training on ambulatory BP.

Cardiovascular Reactivity and IHG Training Responsiveness

IHG training has been shown to elicit BP adaptations in individuals with a high degree of inter-individual variability, which may be related to the cardiovascular reactivity to psychophysical stressors (Somani et al., 2017; Badrov et al., 2013a; Millar et al., 2009). This prospective study demonstrated a novel association between systolic BP reactivity to an IHGT at baseline and reductions in 24 hour systolic ambulatory BP following IHG training in older women. This association was not observed in the younger cohort and may be attributed to the inherently high variability in BP throughout a 24 hour time period in spite of efforts to standardize pre- and post-testing activities of daily living

(Warren et al., 2010).

Furthermore, BP and HR reactivity to the SST and IHGT were not predictive of IHG training-induced adaptations in resting systolic BP in either group. These findings are in stark contrast to work conducted by Millar and colleagues (2009) in the older normotensive population and by Badrov and colleagues (2013b) in hypertensive individuals, who observed associations with systolic BP reactivity to a SST and IHGT to IHG training-induced reductions in resting systolic BP. With respect to the SST, arithmetic tasks have been shown to vary in difficulty (and therefore stress-induction) for individuals depending on factors such as their mathematical intelligence, education level and the perceived importance associated with the task (Maier et al., 2003). Since the present sample consisted of a subset of university students, it is possible their stress-response to the SST may be blunted due to repeated exposure to testing scenarios in school or that participants simply did not associate a level of importance to performing well on the task (Maier et al., 2003).

Somani (2015) observed an association between systolic BP reactivity to an IHGT and IHG training-induced reductions in resting systolic BP in young normotensive men and women. This suggests that, if adequately powered, the present investigation may have observed a similar relationship in the younger cohort with a larger sample.

An association between systolic BP reactivity to an IHGT and reductions in resting systolic BP were observed by Millar and colleagues (2009) in the older normotensive population through a retrospective study design. As such, they could not fully account for sustained IHG training adaptations or other factors during the 6 month de-training period that may have influenced their findings in comparison to the prospective design of the present study. Collectively, these findings suggest that systolic

BP reactivity to an IHGT may be utilized to predict an individual's responsiveness to IHG training, however further research is warranted to determine the efficacy of the use of this stress task as a prescription tool for IHG training.

Further contrasting findings by Badrov and colleagues (2013a), IHG training was not found to attenuate any measures of cardiovascular reactivity in young or older women, however is consistent with findings in the young normotensive population (Somani, 2015). This suggests that a greater contraction stimulus, intervention length and/or training frequency may be required to yield adaptations in cardiovascular reactivity. It is also possible that the present findings support the assumption that cardiovascular reactivity to psychophysical stress tasks is stable over time in healthy individuals (Sherwood et al., 1997).

2.7 Clinical Significance

The findings of this study further promote the use of IHG training as an effective means for young and older, normotensive women to reduce resting BP, while providing the first evidence of its efficacy with respect to ambulatory BP reductions in this population. Evidence for the effectiveness of IHG training in attenuating ambulatory BP is especially striking, considering its superiority as a prognostic indicator of CVD risk particularly in women, who experience a drastic increase in the risk of HTN development following menopause. With the World Health Organization calling for an emphasis on primary prevention of HTN, IHG training continues to rise upon mounting evidence to meet this call to action. Furthermore, the observation of an association between pre-training systolic BP reactivity to an IHGT and post-IHG training reductions in 24 hour ambulatory BP in the older cohort suggests that the IHGT may be a clinically useful tool

for optimizing the prescription of IHG training to those individuals who will benefit most from this intervention.

2.8 References

Badrov, M., Horton, S., Millar, P.J., & McGowan, C.L. (2013a). Cardiovascular stress reactivity tasks successfully predict the hypotensive response of isometric handgrip training in hypertensives. *Psychophysiology, 50,* 407-414.

Badrov, M., Bartol, C., DiBartolomeo, M., Millar, P., McNevin, N., & McGowan, C. (2013b). Effects of isometric handgrip training dose on resting blood pressure and resistance vessel endothelial function in normotensive women. *European Journal of Applied Physiology, 11,* 2091-2100.

Badrov, M., Freeman, S., Zokvic, M., Millar, P., & McGowan, C. (2016). Isometric exercise training lowers resting blood pressure and improves local brachial artery flow-mediated dilation equally in men and women. *European Journal of Physiology, 116,* 1289-1296.

Blumenthal, J.A., Babyak, M.A., Hinderliter, A., Watkins, L.L., Craighead, L., Lin, P.H., Caccia, C., Johnson, J., Waugh, R., & Sherwood, A. (2010). Effects of the DASH diet alone and in combination with exercise and weight loss on blood pressure and cardiovascular biomarkers in men and women with high blood pressure: The ENCORE study. *Archives of Internal Medicine, 170,* 126-135.

Boggia, J., Thijs, L., Hansen, T.W., Li, Y., Kikuya, M., Bjorklund-Bodegard, K., & Staesseon, J.A. (2011). Ambulatory blood pressure monitoring in 9357 subjects from 11 populations highlights missed opportunities for cardiovascular prevention in women. *Hypertension, 57,* 397-405.

Brook, R.D., Appel, L.J., Rubenfire, M., Ogedegbe, G., Bisognano, J.D., Elliott, W.J., Fuchs, F.D., Hughes, J.W., Lackland, D.T., Staffileno, B.A., Townsend, R.R., &

Rajagopalan, S. (2013). Beyond medications and diet: Alternative approaches to lowering blood pressure: A scientific statement from the American Heart Association. *Hypertension, 61,* 1360-1383.

Carlson, D.J., Dieberg, G., Hess, N.C., Millar, P.J., Smart, N.A., et al. (2014). Isometric exercise training for blood pressure management: A systematic review and meta-analysis. *Mayo Clinic Proceedings, 89,* 327-334.

Carlson, D.J., Inder, J., Palanisamy, S.K.A., McFarlane, J.R., Dieberg, G., & Smart, N.A. (2016). The efficacy of isometric resistance training utilizing handgrip exercise for blood pressure management. *Medicine (Baltimore), 95,* e5791.

Chobanian, A., Bakris, G., Black, H., Cushman, W., Green, L., Izzo, Jr. J., Jones, D., Materson, B., Oparil, S., & Wright, Jr J. (2003). Joint national committee on the prevention, detection, and evaluation, and treatment of high blood pressure. National heart, lung, and blood institute; National high blood pressure education program coordinating committee. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension, 42,* 1206-1252.

Colley, R., Garrogiet, D., Janssen, I., Craig, C., Clarke, J., & Tremblay, M. (2011). Physical activity of Canadian adults: Accelerometer results from 2007 to 2009. *Statistics Canada Health Reports, 22,* 7-14.

Devereux, G.R., Wiles, J.D., & Swaine, I.L. (2010). Reductions in resting blood pressure after 4 weeks of isometric exercise training. *European Journal of Applied Physiology, 109,* 601-606.

Dimsdale, J.E., Pierce, C., Schoenfeld, D., Brown, A., Zusman, R., & Graham, R. (1986). Suppressed anger and blood pressure: The effects of race, sex, social class, obesity

and age. *Psychosomatic Medicine, 48,* 430-436.

Gerin, W., Pickering, T.G., Glynn, L., Christenfeld, N., Schwartz, A., Carroll, D., & Davidson, K. (2000). An historical context for behavioral models of hypertension. *Journal of Psychosomatic Research, 48,* 369-377.

Hsia, J., Margolis, K., Eaton, C., Wenger, N., Allison, M., Wu, L., et al. (2007). Prehypertension and cardiovascular disease risk in the women's health initiative. *Circulation, 115,* 855-860.

Inder, J.D., Carlson, D.J., Dieberg, G., McFarlane, J.R., Hess, N.C., & Smart, N.A. (2016). Isometric exercise training for blood pressure management: A systematic review and meta-analysis to optimize benefit. *Hypertension Research, 39,* 88-94.

Jennings, J.R., Karmarck, T., Stewart, C., Eddy, M., & Johnson, P. (1992). Alternate cardiovascular baseline assessment techniques; Vanilla or resting baseline. *Psychophysiology, 29,* 742-750.

Juenger, J., Schellberg, D., Kraemer, S., Haunstetter, A., Zugck, C., Herzog, W., & Haass, M. (2002). Health related quality of life in patients with congestive heart failure: Comparison with other chronic disease and relation to functional variables. *Heart, 87,* 235-241.

Khan et al. (2007). The 2007 Canadian hypertension education program recommendations for the management of hypertension: Part 2 – therapy. *Canadian Journal of Cardiology, 23,* 539-550.

Leung et al. (2016). Hypertension Canada's 2016 hypertension education program guidelines for blood pressure measurement, diagnosis, assessment of risk, prevention and treatment of hypertension. *Canadian Journal of Cardiology, 32,* 569-588.

Llabre, M.M., Spitzer, S.B., Saab, P.G., Ironson, G.H., & Schneiderman, N. (1991). The reliability and specificity of delta versus residualized change as measures of cardiovascular reactivity to behavioural challenges. *Psychophysiology, 28,* 701-711.

Maier, K.J., Waldstein, S.R., & Synowski, S.J. (2003). Relation of cognitive appraisal to cardiovascular reactivity, affect, and task engagement. *Annals of Behavioural Medicine, 26,* 32-41.

McGowan, C.L., Levy, A.S., McCartney, N., & MacDonald, M. (2007a). Isometric handgrip training does not improve flow-mediated dilation in persons with normal blood pressure. *Clinical Science, 12,* 403-409.

McGowan, C.L., Levy, A.S., Millar, P.J., Guzman, J.C., Morillo, C.A., McCartney, N., & MacDonald, M.J. (2006). Acute vascular responses to isometric handgrip exercise and effects of training in persons medicated for hypertension. *American Journal of Phsyiology, 291,* 1797-1802.

McGowan, C.L., Visocchi, A., Faulkner, M., Verduyn, R., Rakobowchuk, M., & Levy, A.S. (2007b). Isometric handgrip training improves local flow-mediated dilation in medicated hypertensives. *European Journal of Applied Physiology, 98,* 355-362.

Millar, P., Bray, S., MacDonald, M., & McCartney, N. (2008). The hypotensive effect of isometric handgrip training using an inexpensive spring handgrip training device. *Journal of Cardiopulmonary Rehabilitation and Prevention, 28,* 203-207.

Millar, P., Bray, S., McGowan, C.L., MacDonald, M., & McCartney, N. (2007). Effects of isometric handgrip training among people medicated for hypertension: A multi-level analysis. *Blood Pressure Monitoring, 12,* 307-314.

Millar, P., MacDonald, M., Bray, S., & McCartney, N. (2009). Cardiovascular reactivity to psycholophysiological stressors: association with hypotensive effects of isometric handgrip training. *Blood Pressure Monitoring, 14,* 190-195.

Millar, P., McGowan, C., Cornelissen, V., Araujo, C., & Swaine, I. (2014). Evidence for the role of isometric exercise training in reducing blood pressure: Potential mechanisms and future directions. *Sports Medicine, 44,* 345-356.

Myers, M.G., Kaczorowski, J., Paterson, J.M., Dolovich, L., & Tu, K. (2015). Thresholds for diagnosing hypertension based on automated office blood pressure measurements and cardiovascular risk. *Hypertension, 66,* 489-495.

O'Brien, E. (2003). Ambulatory blood pressure measurement is indispensable to good clinical practice. *Hypertension, 21,* S11-S18.

Pescatello, L.S., MacDonald, H.V., Lamberti, L., & Johnson, B.T. (2015). Exercise for hypertension: A prescription update integrating existing recommendations with emerging research. *Current Hypertension Reports, 17,* 87.

Pickering, T.G., Shimbo, D., & Haas, D. (2006). Ambulatory blood-pressure monitoring. *New England Journal of Medicine, 354,* 485-501.

Ritchey, M. (2016). Vital signs: Disparities in antihypertensive medication nonadherence among Medicare part D beneficiaries - United States, 2014. *Morbidity and Mortality Weekly Report, 65*.

Schillaci, G., Pirro, M., & Mannarino, E. (2009). Assessing cardiovascular risk. *Circulation, 119,* 210-212.

Schutzer, K.A., & Graves, B.S. (2004). Barriers and motivations to exercise in older adults. *Preventative Medicine, 39,* 1056-1061.

Sherwood, A., Bower, J.K., Routledge, F.S., Blumenthal, J.A., McFetridge-Durdle, J.A.,

Newby, L.K., & Hinderliter, A.L. (2012). Nighttime blood pressure dipping in postmenopausal women with coronary heart disease. *American Journal of Hypertension, 25,* 1077-1082.

Sherwood, A., Girdler, S.S., Bragdon, E.E., West, S.G., Brownley, K.A., Hinderliter, A.L., & Light, K.C. (1997). Ten-year stability of cardiovascular responses to laboratory stressors. *Psychophysiology, 34,* 185-191.

Somani, Y.B. (2015). The effect of a 10 week isometric handgrip training protocol on blood pressure (resting and ambulatory) and cardiovascular reactivity in young, normotensive individuals. *Electronic Theses and Dissertations*, 5285.

Somani, Y.B., Baross, A., Levy, P., Zinszer, K., Milne, K., Swaine, I., & McGowan, C., (2017). Reductions in ambulatory blood pressure in young normotensive men and women after isometric resistance training and its relationship with cardiovascular reactivity. *Blood Pressure Monitoring, 22,* 1-7.

Statistics Canada. (2008). Canadian demographics at a glance. Retrieved from http://www.statcan.gc.ca/pub/91-003-x/2007001/4129907-eng.htm

Statistics Canada. (2014). Health fact sheets. Retrieved from http://www.statcan.gc.ca/pub/82-625-x/2015001/article/14184-eng.htm

Stiller-Moldovan, C., Kenno, K., & McGowan, C.L. (2012b). Effects of isometric handgrip training on blood pressure (resting and 24h ambulatory) and heart rate variability in medicated hypertensive patients. *Blood Pressure Monitoring, 17,* 55-61.

Theriault, L., Stonebridge, C., & Browarski, S. (2010) The Canadian heart health strategy: Risk factors and future cost implications. *The Conference Board of Canada*.

Vasan, R.S., Beiser, A., Seshadri, S., Larson, M.G., Kannel, W.B., D'Agostino, R.B., & Levy, D. (2002). Residual lifetime risk for developing hypertension in middle-aged women and men. The Framingham Heart Study. *Journal of the American Medical Association, 287,* 1003-1010.

Verdecchia, P., Angeli, F., Mazzotta, G., Garofoli, M., Ramundo, E., Gentile, G., Ambrosio, G., & Reboldi, G. (2012). Day-night dip and early-morning surge in blood pressure in hypertension: Prognostic implications. *Hypertension, 60,* 34-42.

Warren, R.E., Marshall, T., Padfield, P.L., & Chrubasik, S. (2010). Variability of office, 24-hour ambulatory, and seld-monitored blood pressure measurements. *British Journal of General Practice, 60,* 675-680.

Wiles, J.D., Coleman, D.A., & Swaine, I.L. The effects of performing isometric training at two exercise intensities in healthy young males. *European Journal of Applied Physiology, 108,* 419-428.

World Health Organization. (2013) A global brief on hypertension; silent killer, global public health crisis. Retrieved from http://www.who.int/cardiovascular_diseases/publications/global_brief_hypertension/en/index.html.

Appendix A: Recruitment Materials

Investigators at the University of Windsor are currently looking for individuals between age 50-80 years with normal blood pressure to participate in a study examining the effects of isometric handgrip exercise on blood pressure, heart rate and blood vessels.

If you are interested and would like more information please contact Mary Ann Zokvic, BSc: (519)-253-3000 ext. 4979 or zokvic@uwindsor.ca

This study has been cleared by the University of Windsor's Research Ethics Board

5	5	5	5	5	5	5	5	5	5	5	5	5
1	1	1	1	1	1	1	1	1	1	1	1	1
9	9	9	9	9	9	9	9	9	9	9	9	9
-	-	-	-	-	-	-	-	-	-	-	-	-
2	2	2	2	2	2	2	2	2	2	2	2	2
5	5	5	5	5	5	5	5	5	5	5	5	5
3	3	3	3	3	3	3	3	3	3	3	3	3
-	-	-	-	-	-	-	-	-	-	-	-	-
3	3	3	3	3	3	3	3	3	3	3	3	3
0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0	0	0	0
ext.	ext.	ext.	ext.	ext.	ext.	ext.	ext.	ext.	ext.	ext.	ext.	ext.
4979	4979	4979	4979	4979	4979	4979	4979	4979	4979	4979	4979	4979

Local media/newspaper/email recruitment script:

"Attention all men and women between age 50-80 years with normal blood pressure. You may be eligible to participate in a research study being conducted by investigators at the University of Windsor. We are investigating the effects of ten weeks of isometric handgrip exercise training on your blood pressure, heart rate and blood vessels. For more information please contact Mary Ann Zokvic at 519-253-3000 ex. 4979 or zokvic@uwindsor.ca."

Appendix B: Consent Form

Title of Study: Isometric Exercise Training and Blood Pressure Regulation: Exploring Sex- and Age-Related Differences

You are asked to participate in a 10-week isometric exercise training research study conducted jointly between the University of Windsor and The University of Northampton (Northampton, England). Your total time commitment for the entire study is ~ 22 hours: a) determining if you qualify to participate in the study (~I hour), b) testing days (~6 hours total), and c) exercise training (~30 minutes, 3X per week; ~15 hours total).

If you have any questions or concerns about the research at the University of Windsor site, please feel to contact Cheri McGowan, PhD (519-253-3000 ext. 2451; mcgowanc@uwindsor.ca), or Kevin Milne, PhD (519-253-3000 ext. 2452; kjmilne@windsor.ca).

PURPOSE OF THE STUDY

Our research groups in Canada and England have shown that isometric (constant squeeze) exercise training using a handgrip (isometric handgrip (IHG) training) and leg machine (isometric leg training) lowers resting blood pressure in younger and older people who have high blood pressure, and even in those with normal blood pressure. However, we do not know why it works. Not all people have a drop in their blood pressure after training, so identifying those people it will help is also important.

The part of the study at the University of Windsor site, will see if certain tasks (e.g., a handgrip squeeze or a simple math test) that raise your heart rate and blood pressure can predict who will have a drop in their resting blood pressure after 10 weeks handgrip training, 3 times a week. In addition, we will test the function of some of your blood vessels, as well as the activity of your nervous system. Our study will also see whether men and women respond differently, and if younger and older people respond differently.

In order to participate in this study you must have a normal blood pressure (<140/90 mmHg). You must be 18-40 years or 50-80 years of age to participate in this study. If you have a disorder or any known ailments or are taking any medications that influence your cardiovascular system you may be ineligible to participate. If you have a physical limitation impairing your ability to exercise you may also be ineligible to participate.

PROCEDURES

If you volunteer to participate in this study, you will be asked to attend the following:

Visit 1 (approximately 30 minutes):

You will meet with the study investigators at the Physical Activity and Cardiovascular Research (PACR) Laboratory (Room #240, Human Kinetics Building, University of Windsor, Windsor, ON, Canada) where you will receive a consent form and information sheet about the study. At this time, one of the study investigators will explain all parts of the study. If you are still interested in participating in the study, you will be asked to sign the consent form and fill out a brief medical questionnaire. You will then have your blood pressure measured in your upper arm, similar to how it is taken at a doctor's office. In brief, your resting blood pressure will be measured in your upper dominant arm after 10 minutes of seated rest. Your blood pressure will be measured 4 times, with 2-minutes of rest between measures.

Visit 2 (approximately 30 minutes):

If you are still interested in participating in the study, and you are initially eligible after Visit 1, you will visit the lab again. First, you will have your resting blood pressure measured again, in the same manner as the first visit. If your blood pressure is still <140/90 mmHg, you will then practice all parts of the study including the math task and the handgrip exercise. After you practice all parts of the study, you will be asked to complete a physical activity readiness questionnaire called a PAR-Q, and if needed, a more detailed form called the PAR-MedX. You will also receive two letters to be taken to your health care provider. One will notify your health care provider of your involvement in the study and the second is to be signed by your health care provider and returned to us. Upon receiving this document you will then choose the dates to complete the 3 days of testing. All testing days will be separated by at least 24 hours.

Testing Days (Visits 3-4):

You will be asked not to exercise vigorously (e.g., exercise that causes you to breath really hard and sweat heavily) or drink alcohol for 24 hours before each testing day, and to avoid caffeine for at least 12 hours before. All testing will take place at the same time of day, in a quiet, temperature-controlled room, following a light meal for visit 3 and 4 hours after eating for visit 4. On testing days, you will be asked to go to the washroom before testing, as a full bladder can increase your blood pressure.

All 3 testing days will happen again after 10 weeks of handgrip training (Week 11). You will train 3 times per week, for a total of 10 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. All training sessions will be supervised by an exercise trainer, where your resting blood pressure and heart rate will be measured before each session. Training sessions should not last longer than 30 minutes. Your exercise, nutritional, and medication habits (where necessary) will be monitored in exercise log books throughout the study to make sure they do not change.

Visit 3 (approximately 3 hours):

Upon entering the lab you will complete a Depression Anxiety Stress Scales questionnaire. Your resting blood pressure and heart rate will also be measured in the same way that it was measured in the previous visits. After that, your blood pressure and heart rate will be measured continuously for 10 minutes. Continuous blood pressure will be measured by a small cuff placed around your middle finger on your dominant hand, and continuous heart rate will be measured by using 3 sticker electrodes that will be placed on your chest.

After that, we will remove the finger blood pressure cuff, but the cuff on your upper arm and the sticker electrodes on your chest will stay in place. You will then perform 2 tasks in random order (i.e., chosen by chance). These include: 1) a short handgrip exercise, and 2) a math task.

The short handgrip task will involve you performing a single 2-minute squeeze at 30% of your maximum squeeze on a computerized handgrip using your non-dominant hand. The math task will involve looking at a computer and subtracting a 2-digit number from a 4-digit number displayed and responding with your answer aloud. You will be shown 25 numbers in total and will have 5 seconds answer each one. Heart rate and blood pressure (every minute) will be measured during and after each task, and once both heart rate and blood pressure have stabilized, you will begin the next task.

At the end of the testing session, we will send you home with a machine that will record your blood pressure for the next 24 hours. You will also be given a sheet to track your activity during this 24 hour time as well as your diet for the past three days. The morning following, you will return this device to us and once again complete the Depression Anxiety Stress Scales questionnaire.

Visit 4 (approximately 3 hours):

First, your resting blood pressure and heart rate will be measured in the same way as it was on your other visits.

Next, we will take a picture of an artery in your heart using an ultrasound probe placed over your heart. Following this, a small ultrasound wand will be placed over your heart and in the notch above your breast bone to measure the amount of blood pumped from your heart.

Next, while seated, a cuff will be placed on your non-dominant forearm. A technique called flow-mediated dilation will be used on your upper non-dominant arm to measure the size of your artery and the speed of blood flowing through it. To do this a probe with ultrasound gel will be placed on your upper arm. The cuff on your forearm will be inflated to ~200 mmHg for 5 minutes and then released.

After 30 minutes of rest, blood vessel function will be measured using a technique called

venous strain-gauge plethysmography. In this procedure, your dominant arm will be elevated above heart level and a rubber strain gauge (similar to an elastic band) will be placed around the largest part of your forearm. A cuff will be placed on your wrist and will be inflated to a pressure above systolic BP (generally close to 200 mmHg). The cuff on your upper arm will be inflated to ~40 – 60 mmHg for 10 seconds and then released for 5 seconds, and this will continue for 1 minute. Next, the upper arm cuff will be inflated to 200 mmHg for 5 minutes and then released. Forearm blood flow will be measured every 10 seconds for 1 minute after the cuff is released.

You will then perform a bout of isometric handgrip exercise. You will squeeze the handgrip 4 times, holding it at 30% of your maximum squeeze for 2 minutes, and switching back and forth between hands (e.g., right hand squeeze for 2 minutes, left hand squeeze for 2 minutes, then another right hand squeeze and another left hand squeeze). You will have a minute to rest between each squeeze. Your blood pressure and heart rate will be measured throughout. We will also measure blood flow in your upper non-dominant arm using the ultrasound as we did before, and blood flow from your heart by holding a small ultrasound wand in the notch above your breast bone.

You will be asked to rate how hard you feel you are working on a scale of 1 to 10 repeatedly throughout the exercise. Following the exercise, the flow-mediated dilation and venous strain-gauge plethysmography procedures will be repeated.

Visit 5 (approximately 30 minutes) - OPTIONAL:

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), and oxidative stress (chemical reaction which can have a negative effect on many cells of the body including the heart and blood vessels).

Training Days (approximately 30 minutes)

You will visit the laboratory 3 times per week, for a total of 10 weeks. The handgrip exercise will be identical to the one you performed on Visit 4 (4, 2 minute squeezes, switching hands with each squeeze, with a minute of rest between). Again, squeezes will be performed at 30% of your hardest squeeze. All of your sessions will be monitored by an exercise trainer, and your blood pressure and heart rate will be measured before each session, the same way as described above. We will monitor any changes in diet, exercise or medication at each visit.

POTENTIAL RISKS AND DISCOMFORTS

You may experience tendonitis in the tendons of the exercising arms with handgrip exercise however this risk is low if the exercise is properly performed. You may experience numbness and/or tingling in your arm or hand while the cuff(s) are inflated during our measurements. The gel used to image your blood vessels and/or the sticker-

electrodes used to measure your heart rate may cause a rash, but this does not happen often. If you choose to participate in the blood sampling portion of the study, the blood draws will be taken by a registered nurse under completely sterile conditions. You may experience some local discomfort when the needle is inserted, and there is a small risk of infection. However, once the needle is removed, pressure will be placed on the site in order to have as little bruising as possible.

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. Study investigators will reinforce proper exercise technique throughout the study. If you experience any adverse effects during any testing procedure, emergency responses will be provided.

POTENTIAL BENEFITS TO PARTICIPANTS 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 other parts of your cardiovascular system (e.g., reduced tension in certain blood vessels of your body).

If we prove our theories, isometric handgrip training may be a possible exercise option to lower blood pressure.

COMPENSATION FOR PARTICIPATION

You will receive a Human Kinetics T-shirt for your participation.

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), with the exception of the medical and physical activity readiness questionnaires. All paper 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 after 5 years.

PARTICIPATION AND WITHDRAWAL

You can choose whether to be in this study or not, and your participation or lack of it will not influence your participation in another study. 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 PARTICIPANTS

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

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

RIGHTS OF RESEARCH PARTICIPANTS

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, ON, N9B 3P4; Telephone: 519-253-3000, ext. 3948; e-mail: ethics@uwindsor.ca

SIGNATURE OF RESEARCH PARTICIPANT/LEGAL REPRESENTATIVE
I understand the information provided for the study "Isometric exercise training and blood pressure regulation: exploring sex- and age-related differences" 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 Participant

_____ _____
Signature of Participant Date

SIGNATURE OF INVESTIGATOR
These are the terms under which I will conduct research.

_____ _____
Signature of Investigator Date

Appendix C: Letter of Information

Title of Study: Isometric Exercise Training and Blood Pressure Regulation: Exploring Sex- and Age-Related Differences

You are asked to participate in a 10-week isometric exercise training research study conducted jointly between the University of Windsor and The University of Northampton (Northampton, England). Your total time commitment for the entire study is ~ 22 hours: a) determining if you qualify to participate in the study (~I hour), b) testing days (~6 hours total), and c) exercise training (~30 minutes, 3X per week; ~15 hours total).

If you have any questions or concerns about the research at the University of Windsor site, please feel to contact Cheri McGowan, PhD (519-253-3000 ext. 2451; mcgowanc@uwindsor.ca), or Kevin Milne, PhD (519-253-3000 ext. 2452; kjmilne@windsor.ca).

PURPOSE OF THE STUDY

Our research groups in Canada and England have shown that isometric (constant squeeze) exercise training using a handgrip (isometric handgrip (IHG) training) and leg machine (isometric leg training) lowers resting blood pressure in younger and older people who have high blood pressure, and even in those with normal blood pressure. However, we do not know why it works. Not all people have a drop in their blood pressure after training, so identifying those people it will help is also important.

The part of the study at the University of Windsor site, will see if certain tasks (e.g., a handgrip squeeze or a simple math test) that raise your heart rate and blood pressure can predict who will have a drop in their resting blood pressure after 10 weeks handgrip training, 3 times a week. In addition, we will test the function of some of your blood vessels, as well as the activity of your nervous system. Our study will also see whether men and women respond differently, and if younger and older people respond differently.

In order to participate in this study you must have a normal blood pressure (<140/90 mmHg). You must be 18-40 years or 50-80 years of age to participate in this study. If you have a disorder or any known ailments or are taking any medications that influence your cardiovascular system you may be ineligible to participate. If you have a physical limitation impairing your ability to exercise you may also be ineligible to participate.

PROCEDURES

If you volunteer to participate in this study, you will be asked to attend the following:

Visit 1 (approximately 30 minutes):

You will meet with the study investigators at the Physical Activity and Cardiovascular Research (PACR) Laboratory (Room #240, Human Kinetics Building, University of Windsor, Windsor, ON, Canada) where you will receive a consent form and information sheet about the study. At this time, one of the study investigators will explain all parts of the study. If you are still interested in participating in the study, you will be asked to sign the consent form and fill out a brief medical questionnaire. You will then have your blood pressure measured in your upper arm, similar to how it is taken at a doctor's office. In brief, your resting blood pressure will be measured in your upper dominant arm after 10 minutes of seated rest. Your blood pressure will be measured 4 times, with 2-minutes of rest between measures.

Visit 2 (approximately 30 minutes):

If you are still interested in participating in the study, and you are initially eligible after Visit 1, you will visit the lab again. First, you will have your resting blood pressure measured again, in the same manner as the first visit. If your blood pressure is still <140/90 mmHg, you will then practice all parts of the study including the math task and the handgrip exercise. After you practice all parts of the study, you will be asked to complete a physical activity readiness questionnaire called a PAR-Q, and if needed, a more detailed form called the PAR-MedX. You will also receive two letters to be taken to your health care provider. One will notify your health care provider of your involvement in the study and the second is to be signed by your health care provider and returned to us. Upon receiving this document you will then choose the dates to complete the 3 days of testing. All testing days will be separated by at least 24 hours.

Testing Days (Visits 3-4):

You will be asked not to exercise vigorously (e.g., exercise that causes you to breath really hard and sweat heavily) or drink alcohol for 24 hours before each testing day, and to avoid caffeine for at least 12 hours before. All testing will take place at the same time of day, in a quiet, temperature-controlled room, following a light meal for visit 3 and 4 hours after eating for visit 4. On testing days, you will be asked to go to the washroom before testing, as a full bladder can increase your blood pressure.

All 3 testing days will happen again after 10 weeks of handgrip training (Week 11). You will train 3 times per week, for a total of 10 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. All training sessions will be supervised by an exercise trainer, where your resting blood pressure and heart rate will be measured before each session. Training sessions should not last longer than 30 minutes. Your exercise, nutritional, and medication habits (where necessary) will be monitored in exercise log books throughout the study to make sure they do not change.

Visit 3 (approximately 3 hours):

Upon entering the lab you will complete a Depression Anxiety Stress Scales questionnaire. Your resting blood pressure and heart rate will also be measured in the same way that it was measured in the previous visits. After that, your blood pressure and heart rate will be measured continuously for 10 minutes. Continuous blood pressure will be measured by a small cuff placed around your middle finger on your dominant hand, and continuous heart rate will be measured by using 3 sticker electrodes that will be placed on your chest.

After that, we will remove the finger blood pressure cuff, but the cuff on your upper arm and the sticker electrodes on your chest will stay in place. You will then perform 2 tasks in random order (i.e., chosen by chance). These include: 1) a short handgrip exercise, and 2) a math task.

The short handgrip task will involve you performing a single 2-minute squeeze at 30% of your maximum squeeze on a computerized handgrip using your non-dominant hand. The math task will involve looking at a computer and subtracting a 2-digit number from a 4-digit number displayed and responding with your answer aloud. You will be shown 25 numbers in total and will have 5 seconds answer each one. Heart rate and blood pressure (every minute) will be measured during and after each task, and once both heart rate and blood pressure have stabilized, you will begin the next task.

At the end of the testing session, we will send you home with a machine that will record your blood pressure for the next 24 hours. You will also be given a sheet to track your activity during this 24 hour time as well as your diet for the past three days. The morning following, you will return this device to us and once again complete the Depression Anxiety Stress Scales questionnaire.

Visit 4 (approximately 3 hours):

First, your resting blood pressure and heart rate will be measured in the same way as it was on your other visits.

Next, we will take a picture of an artery in your heart using an ultrasound probe placed over your heart. Following this, a small ultrasound wand will be placed over your heart and in the notch above your breast bone to measure the amount of blood pumped from your heart.

Next, while seated, a cuff will be placed on your non-dominant forearm. A technique called flow-mediated dilation will be used on your upper non-dominant arm to measure the size of your artery and the speed of blood flowing through it. To do this a probe with ultrasound gel will be placed on your upper arm. The cuff on your forearm will be inflated to ~200 mmHg for 5 minutes and then released.

After 30 minutes of rest, blood vessel function will be measured using a technique called venous strain-gauge plethysmography. In this procedure, your dominant arm will be elevated above heart level and a rubber strain gauge (similar to an elastic band) will be placed around the largest part of your forearm. A cuff will be placed on your wrist and

will be inflated to a pressure above systolic BP (generally close to 200 mmHg). The cuff on your upper arm will be inflated to ~40 – 60 mmHg for 10 seconds and then released for 5 seconds, and this will continue for 1 minute. Next, the upper arm cuff will be inflated to 200 mmHg for 5 minutes and then released. Forearm blood flow will be measured every 10 seconds for 1 minute after the cuff is released.

You will then perform a bout of isometric handgrip exercise. You will squeeze the handgrip 4 times, holding it at 30% of your maximum squeeze for 2 minutes, and switching back and forth between hands (e.g., right hand squeeze for 2 minutes, left hand squeeze for 2 minutes, then another right hand squeeze and another left hand squeeze). You will have a minute to rest
between each squeeze. Your blood pressure and heart rate will be measured throughout. We will also measure blood flow in your upper non-dominant arm using the ultrasound as we did
before, and blood flow from your heart by holding a small ultrasound wand in the notch above your breast bone.

You will be asked to rate how hard you feel you are working on a scale of 1 to 10 repeatedly throughout the exercise. Following the exercise, the flow-mediated dilation and venous strain-gauge plethysmography procedures will be repeated.

Visit 5 (approximately 30 minutes) - OPTIONAL:

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), and oxidative stress (chemical reaction which can have a negative effect on many cells of the body including the heart and blood vessels).

Training Days (approximately 30 minutes)

You will visit the laboratory 3 times per week, for a total of 10 weeks. The handgrip exercise will be identical to the one you performed on Visit 4 (4, 2 minute squeezes, switching hands with each squeeze, with a minute of rest between). Again, squeezes will be performed at 30% of your hardest squeeze. All of your sessions will be monitored by an exercise trainer, and your blood pressure and heart rate will be measured before each session, the same way as described above. We will monitor any changes in diet, exercise or medication at each visit.

POTENTIAL RISKS AND DISCOMFORTS

You may experience tendonitis in the tendons of the exercising arms with handgrip exercise however this risk is low if the exercise is properly performed. You may experience numbness and/or tingling in your arm or hand while the cuff(s) are inflated during our measurements. The gel used to image your blood vessels and/or the sticker-electrodes used to measure your heart rate may cause a rash, but this does not happen

often. If you choose to participate in the blood sampling portion of the study, the blood draws will be taken by a registered nurse under completely sterile conditions. You may experience some local discomfort when the needle is inserted, and there is a small risk of infection. However, once the needle is removed, pressure will be placed on the site in order to have as little bruising as possible.

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. Study investigators will reinforce proper exercise technique throughout the study. If you experience any adverse effects during any testing procedure, emergency responses will be provided.

POTENTIAL BENEFITS TO PARTICIPANTS 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 other parts of your cardiovascular system (e.g., reduced tension in certain blood vessels of your body).

If we prove our theories, isometric handgrip training may be a possible exercise option to lower blood pressure.

COMPENSATION FOR PARTICIPATION

You will receive a Human Kinetics T-shirt for your participation.

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), with the exception of the medical and physical activity readiness questionnaires. All paper 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 after 5 years.

PARTICIPATION AND WITHDRAWAL

You can choose whether to be in this study or not, and your participation or lack of it will not influence your participation in another study. 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 PARTICIPANTS

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

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

RIGHTS OF RESEARCH PARTICIPANTS

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, ON, N9B 3P4; Telephone: 519-253-3000, ext. 3948; e-mail: ethics@uwindsor.ca

SIGNATURE OF RESEARCH PARTICIPANT/LEGAL REPRESENTATIVE
I understand the information provided for the study "Isometric exercise training and blood pressure regulation: exploring sex- and age-related differences" 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.

SIGNATURE OF INVESTIGATOR
These are the terms under which I will conduct research.

_____ _____

Signature of Investigator Date

Appendix D: Medical Questionnaire

Last Name _____ First Name _____
Height:_____ Weight: _____
Date of Birth (Month/Yr) _____
Phone (_____) _____ Postal Code _____

FOR EMERGENCY NOTIFY:
Name_____ Relationship _____
Address _____
Phone_____
Family Doctor's Name _____
Date of Last Physical _____

Please Circle Yes or No:

1. Have you ever been hospitalized?
YES NO If yes, please specify?

_____

Have you ever had surgery?
YES NO If yes, please specify?

_____

2. Are you presently taking any medications or pills (including aspirin and other over-the-counter medication)?
YES NO If yes, please specify?

_____

Are you presently taking any vitamins, supplements, and/or herbal supplements?
YES NO If yes, please specify?

_____

3. Do you have any allergies (medicine, food, bees or other stinging insects)?
YES NO If yes, please specify?

---

4. Have you ever passed out during or after exercise?
   YES NO
   Have you ever been dizzy during or after exercise?
   YES NO
   Have you ever had chest pain during or after exercise?
   YES NO
   Do you have high blood pressure (hypertension) or low blood pressure (hypotension)?
   YES NO
   Have you ever been told that you have a kidney problem?
   YES NO
   Have you ever been told that you have joint instability?
   YES NO
   Have you ever been told that you have a stomach problem?
   YES NO
   Have you ever been told that you have a heart problem?
   YES NO
   Have you ever been told that you have a heart murmur?
   YES NO
   Do you have a machine that regulated your heart beat?
   YES NO
   Have you ever had racing of your heart or skipped heartbeats?
   YES NO
   Has anyone in your family died of heart problems or a sudden death before age 50?
   YES NO

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

YES NO If yes, please specify?

If you get a cut, does it take you a long time to stop bleeding?
YES NO
If you experience a blow to a muscle, do you bruise easily?
YES NO

6. Do you have Diabetes?

YES NO

7. Do you have Asthma or any other breathing problems?

YES NO If yes, please specify?

_____

8. Do you have any type of cardiovascular disease?
YES NO If yes, please specify?

_____

9. Have you had any other medical problems (infectious mononucleosis, etc.)?
YES NO If yes, please specify?

_____

10. Have you had any medical problems since your last physical?
YES NO If yes, please specify?

_____

11. Do you smoke?
YES NO

12. Do you aerobically exercise (e.g., walking) for $\geq$ 30 minutes, > 2 times per week?
YES NO

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

If applicable, please indicate your last date of menstruation:

_____

Appendix E: Resting BP and HR Device

Dinamap Carescape v100, Critikon, Tampa, Florida, USA

Appendix F: Physical Activity Readiness Questionnaire

Physical Activity Readiness Questionnaire - PAR-Q (revised 2002)

PAR-Q & YOU

(A Questionnaire for People Aged 15 to 69)

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. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly: check YES or NO.

YES	NO		
☐	☐	1.	**Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?**
☐	☐	2.	**Do you feel pain in your chest when you do physical activity?**
☐	☐	3.	**In the past month, have you had chest pain when you were not doing physical activity?**
☐	☐	4.	**Do you lose your balance because of dizziness or do you ever lose consciousness?**
☐	☐	5.	**Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?**
☐	☐	6.	**Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?**
☐	☐	7.	**Do you know of any other reason why you should not do physical activity?**

If you answered

YES to one or more questions

Talk with your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want — as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/94, talk with your doctor before you start becoming much more physically active.

→

DELAY BECOMING MUCH MORE ACTIVE:

- if you are not feeling well because of a temporary illness such as a cold or a fever – wait until you feel better; or
- if you are or may be pregnant – talk to your doctor before you start becoming more active.

PLEASE NOTE: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

Informed Use of the PAR-Q: The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity, and if in doubt after completing this questionnaire, consult your doctor prior to physical activity.

No changes permitted. You are encouraged to photocopy the PAR-Q but only if you use the entire form.

NOTE: If the PAR-Q is being given to a person before he or she participates in a physical activity program or a fitness appraisal, this section may be used for legal or administrative purposes.

"I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction."

NAME _____

SIGNATURE _____ DATE _____

SIGNATURE OF PARENT or GUARDIAN (for participants under the age of majority) _____ WITNESS _____

Note: This physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if your condition changes so that you would answer YES to any of the seven questions.

Supported by: Health Canada Santé Canada

continued on other side...

Appendix G: PARmed-X

Physical Activity Readiness Medical Examination (revised 2002)

PARmed-X PHYSICAL ACTIVITY READINESS MEDICAL EXAMINATION

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 Certified Exercise Physiologist®. 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. _____

B PAR-Q: Please indicate the PAR-Q questions to which you answered YES

- ❑ Q 1 Heart condition
- ❑ Q 2 Chest pain during activity
- ❑ Q 3 Chest pain at rest
- ❑ Q 4 Loss of balance, dizziness
- ❑ Q 5 Bone or joint problem
- ❑ Q 6 Blood pressure or heart drugs
- ❑ Q 7 Other reason:

_____

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.*

D PHYSICAL ACTIVITY INTENTIONS:

What physical activity do you intend to do?

_____

_____

_____

This section to be completed by the examining physician

Physical Exam:

Ht	Wt	BP i) /
		BP ii) /

Conditions limiting physical activity:

- ❑ Cardiovascular
- ❑ Musculoskeletal
- ❑ Respiratory
- ❑ Abdominal
- ❑ Other

Tests required:

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

Physical Activity Readiness Conveyance/Referral:

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

Further Information:
- ❑ Attached
- ❑ To be forwarded
- ❑ Available on request

- ❑ 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 Certified Exercise Physiologist®
- ❑ Unrestricted physical activity–start slowly and build up gradually

Supported by: Health Canada Santé Canada

1

Physical Activity Readiness
Medical Examination
(revised 2002)

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 69. 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.

	Absolute Contraindications	Relative Contraindications	Special Prescriptive Conditions	ADVICE
	Permanent restriction or temporary restriction until condition is treated, stable, and/or past acute phase.	Highly variable. Value of exercise testing and/or program may exceed risk. Activity may be restricted. Desirable to maximize control of condition. Direct or indirect medical supervision of exercise program may be desirable.	Individualized prescriptive advice generally appropriate: • limitations imposed; and/or • special exercises prescribed. May require medical monitoring and/or initial supervision in exercise program.	
Cardiovascular	❑ aortic aneurysm (dissecting) ❑ aortic stenosis (severe) ❑ congestive heart failure ❑ crescendo angina ❑ myocardial infarction (acute) ❑ myocarditis (active or recent) ❑ pulmonary or systemic embolism—acute ❑ thrombophlebitis ❑ ventricular tachycardia and other dangerous dysrhythmias (e.g., multi-focal ventricular activity)	❑ aortic stenosis (moderate) ❑ subaortic stenosis (severe) ❑ marked cardiac enlargement ❑ supraventricular dysrhythmias (uncontrolled or high rate) ❑ ventricular ectopic activity (repetitive or frequent) ❑ ventricular aneurysm ❑ hypertension—untreated or uncontrolled severe (systemic or pulmonary) ❑ hypertrophic cardiomyopathy ❑ compensated congestive heart failure	❑ aortic (or pulmonary) stenosis—mild angina pectoris and other manifestations of coronary insufficiency (e.g., post-acute infarct) ❑ cyanotic heart disease ❑ shunts (intermittent or fixed) ❑ conduction disturbances • complete AV block • left BBB • Wolff-Parkinson-White syndrome ❑ dysrhythmias—controlled ❑ fixed rate pacemakers	• clinical exercise test may be warranted in selected cases, for specific determination of functional capacity and limitations and precautions (if 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).
			❑ intermittent claudication	progressive exercise to tolerance
			❑ hypertension: systolic 160-180; diastolic 105+	progressive exercise; care with medications (serum electrolytes; post-exercise syncope; etc.)
Infections	❑ acute infectious disease (regardless of etiology)	❑ subacute/chronic/recurrent infectious diseases (e.g., malaria, others)	❑ chronic infections ❑ HIV	variable as to condition
Metabolic		❑ uncontrolled metabolic disorders (diabetes mellitus, thyrotoxicosis, myxedema)	❑ renal, hepatic & other metabolic insufficiency	variable as to status
			❑ obesity ❑ single kidney	dietary moderation, and initial light exercises with slow progression (walking, swimming, cycling)
Pregnancy		❑ complicated pregnancy (e.g., toxemia, hemorrhage, incompetent cervix, etc.)	❑ advanced pregnancy (late 3rd trimester)	refer to the "PARmed-X for PREGNANCY"

References:

Arraix, G.A., Wigle, D.T., Mao, Y. (1992). Risk Assessment of Physical Activity and Physical Fitness in the Canada Health Survey Follow-Up Study. **J. Clin. Epidemiol.** 45:4 419-428.

Mottola, M., Wolfe, L.A. (1994). Active Living and Pregnancy. In: A. Quinney, L. Gauvin, T. Wall (eds.), **Toward Active Living: Proceedings of the International Conference on Physical Activity, Fitness and Health**. Champaign, IL: Human Kinetics.

PAR-Q Validation Report, British Columbia Ministry of Health, 1978.

Thomas, S., Reading, J., Shephard, R.J. (1992). Revision of the Physical Activity Readiness Questionnaire (PAR-Q). **Can. J. Spt. Sci.** 17: 4 338-345.

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

Disponible en français sous le titre
«Évaluation médicale de l'aptitude à l'activité physique (X-AAP)»

Continued on page 3...

Physical Activity Readiness
Medical Examination
(revised 2002)

	Special Prescriptive Conditions	ADVICE
Lung	❑ chronic pulmonary disorders	special relaxation and breathing exercises
	❑ obstructive lung disease ❑ asthma	breath control during endurance exercises to tolerance; avoid polluted air
	❑ exercise-induced bronchospasm	avoid hyperventilation during exercise; avoid extremely cold conditions; warm up adequately; utilize appropriate medication.
Musculoskeletal	❑ low back conditions (pathological, functional)	avoid or minimize exercise that precipitates or exasperates e.g., forced extreme flexion, extension, and violent twisting; correct posture, proper back exercises
	❑ arthritis—acute (infective, rheumatoid; gout)	treatment, plus judicious blend of rest, splinting and gentle movement
	❑ arthritis—subacute	progressive increase of active exercise therapy
	❑ arthritis—chronic (osteoarthritis and above conditions)	maintenance of mobility and strength; non-weightbearing exercises to minimize joint trauma (e.g., cycling, aquatic activity, etc.)
	❑ orthopaedic	highly variable and individualized
	❑ hernia	minimize straining and isometrics; stregthen abdominal muscles
	❑ osteoporosis or low bone density	avoid exercise with high risk for fracture such as push-ups, curl-ups, vertical jump and trunk forward flexion; engage in low-impact weight-bearing activities and resistance training
CNS	❑ convulsive disorder not completely controlled by medication	minimize or avoid exercise in hazardous environments and/or exercising alone (e.g., swimming, mountainclimbing, etc.)
	❑ recent concussion	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
Blood	❑ anemia—severe (< 10 Gm/dl) ❑ electrolyte disturbances	control preferred; exercise as tolerated
Medications	❑ antianginal ❑ antiarrhythmic ❑ antihypertensive ❑ anticonvulsant ❑ beta-blockers ❑ digitalis preparations ❑ diuretics ❑ ganglionic blockers ❑ others	NOTE: consider underlying condition. Potential for: exertional syncope, electrolyte imbalance, bradycardia, dysrhythmias, impaired coordination and reaction time, heat intolerance. May alter resting and exercise ECG's and exercise test performance.
Other	❑ post-exercise syncope	moderate program
	❑ heat intolerance	prolong cool-down with light activities; avoid exercise in extreme heat
	❑ temporary minor illness	postpone until recovered
	❑ cancer	if potential metastases, test by cycle ergometry, consider non-weight bearing exercises; exercise at lower end of prescriptive range (40-65% of heart rate reserve), depending on condition and recent treatment (radiation, chemotherapy); monitor hemoglobin and lymphocyte counts; add dynamic lifting exercise to strengthen muscles, using machines rather than weights.

*Refer to special publications for elaboration as required

The following companion forms are available online: www.csep.ca/publications

The **Physical Activity Readiness Questionnaire (PAR-Q)** - a questionnaire for people aged 15-69 to complete before becoming much more physically active. Please return the completed form to the participant or his/her physical activity professional.

The **Physical Activity Readiness Medical Examination for Pregnancy (PARmed-X for PREGNANCY)** - to be used by physicians with pregnant patients who wish to become more physically active. Please return the completed form to the participant or his/her physical activity professional.

For more information, please contact the:

Canadian Society for Exercise Physiology
370-18 Louisa Street
Ottawa, Ontario K1R 6Y6
Tel. 1-877-651-3755 • Online: www.csep.ca

Note to physical activity professionals...

It is a prudent practice to retain the completed Physical Activity Readiness Conveyance/Referral Form in the participant's file.

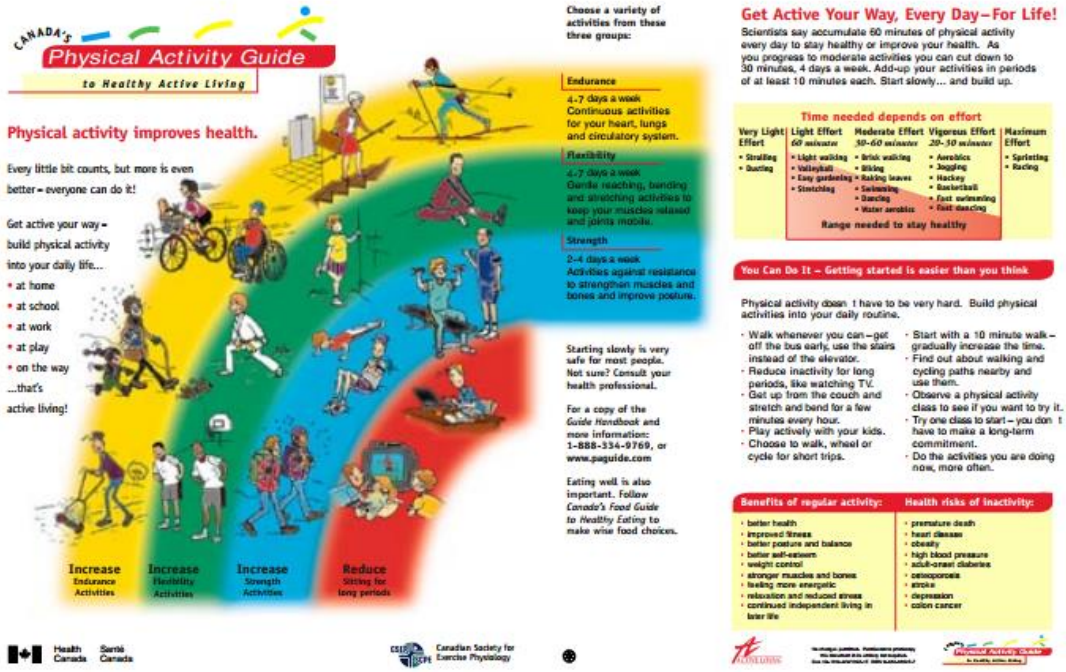
Supported by: Health Canada Santé Canada

Continued on page 4...

3

Physical Activity Readiness
Medical Examination
(revised 2002)

PARmed-X PHYSICAL ACTIVITY READINESS MEDICAL EXAMINATION



Source: Canada's Physical Activity Guide to Healthy Active Living, Health Canada, 1998 http://www.hc-sc.gc.ca/hppb/paguide/pdf/guideEng.pdf

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 Certified Exercise Physiologist®
- ❑ Unrestricted physical activity — start slowly and build up gradually

Further Information:
- ❑ Attached
- ❑ To be forwarded
- ❑ Available on request

Physician/clinic stamp:

_____ M.D.

_____ 20_____
(date)

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.

4

Appendix H: Health Care Provider Document

Date: _____.

Dear _____,

Your patient, _____, has expressed interest in participating in our research study in the Department of Kinesiology at the University of Windsor entitled: Isometric Exercise Training and Blood Pressure Regulation: Exploring Sex- and Age-Related Differences (see attached Letter of Information for Consent for details). We ask that you sign the attached form and return it to us, along with the PARmed-X (where applicable).

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. Cheri McGowan, PhD
Dr. Kevin Milne, PhD
Assistant Professors
Department of Kinesiology
Faculty of Human Kinetics
University of Windsor

Date: _____.

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 Exercise Training and Blood Pressure Regulation: Exploring Sex- and Age-Related Differences. I have approved my patient's participation in your study.

_____

Appendix I: DASS and State Trait Questionnaire

DASS

Name: *Date:*

Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you *over the past week*. There are no right or wrong answers. Do not spend too much time on any statement.

The rating scale is as follows:

0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree, or a good part of time
3 Applied to me very much, or most of the time

1	I found myself getting upset by quite trivial things	0	1	2	3
2	I was aware of dryness of my mouth	0	1	2	3
3	I couldn't seem to experience any positive feeling at all	0	1	2	3
4	I experienced breathing difficulty (eg, excessively rapid breathing, breathlessness in the absence of physical exertion)	0	1	2	3
5	I just couldn't seem to get going	0	1	2	3
6	I tended to over-react to situations	0	1	2	3
7	I had a feeling of shakiness (eg, legs going to give way)	0	1	2	3
8	I found it difficult to relax	0	1	2	3
9	I found myself in situations that made me so anxious I was most relieved when they ended	0	1	2	3
10	I felt that I had nothing to look forward to	0	1	2	3
11	I found myself getting upset rather easily	0	1	2	3
12	I felt that I was using a lot of nervous energy	0	1	2	3
13	I felt sad and depressed	0	1	2	3
14	I found myself getting impatient when I was delayed in any way (eg, lifts, traffic lights, being kept waiting)	0	1	2	3
15	I had a feeling of faintness	0	1	2	3
16	I felt that I had lost interest in just about everything	0	1	2	3
17	I felt I wasn't worth much as a person	0	1	2	3
18	I felt that I was rather touchy	0	1	2	3
19	I perspired noticeably (eg, hands sweaty) in the absence of high temperatures or physical exertion	0	1	2	3
20	I felt scared without any good reason	0	1	2	3
21	I felt that life wasn't worthwhile	0	1	2	3

Please turn the page ☞

Reminder of rating scale:

0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree, or a good part of time
3 Applied to me very much, or most of the time

22	I found it hard to wind down	0	1	2	3
23	I had difficulty in swallowing	0	1	2	3
24	I couldn't seem to get any enjoyment out of the things I did	0	1	2	3
25	I was aware of the action of my heart in the absence of physical exertion (eg, sense of heart rate increase, heart missing a beat)	0	1	2	3
26	I felt down-hearted and blue	0	1	2	3
27	I found that I was very irritable	0	1	2	3
28	I felt I was close to panic	0	1	2	3
29	I found it hard to calm down after something upset me	0	1	2	3
30	I feared that I would be "thrown" by some trivial but unfamiliar task	0	1	2	3
31	I was unable to become enthusiastic about anything	0	1	2	3
32	I found it difficult to tolerate interruptions to what I was doing	0	1	2	3
33	I was in a state of nervous tension	0	1	2	3
34	I felt I was pretty worthless	0	1	2	3
35	I was intolerant of anything that kept me from getting on with what I was doing	0	1	2	3
36	I felt terrified	0	1	2	3
37	I could see nothing in the future to be hopeful about	0	1	2	3
38	I felt that life was meaningless	0	1	2	3
39	I found myself getting agitated	0	1	2	3
40	I was worried about situations in which I might panic and make a fool of myself	0	1	2	3
41	I experienced trembling (eg, in the hands)	0	1	2	3
42	I found it difficult to work up the initiative to do things	0	1	2	3

SELF-EVALUATION QUESTIONNAIRE STAI Form Y-1

Please provide the following information:

Name_____Date_____S_____

Age_____ Gender (*Circle*) **M** **F** T_____

DIRECTIONS:

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you feel *right* now, that is, *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	NOT AT ALL	SOMEWHAT	MODERATELY SO	VERY MUCH SO
1. I feel calm	1	2	3	4
2. I feel secure	1	2	3	4
3. I am tense	1	2	3	4
4. I feel strained	1	2	3	4
5. I feel at ease	1	2	3	4
6. I feel upset	1	2	3	4
7. I am presently worrying over possible misfortunes	1	2	3	4
8. I feel satisfied	1	2	3	4
9. I feel frightened	1	2	3	4
10. I feel comfortable	1	2	3	4
11. I feel self-confident	1	2	3	4
12. I feel nervous	1	2	3	4
13. I am jittery	1	2	3	4
14. I feel indecisive	1	2	3	4
15. I am relaxed	1	2	3	4
16. I feel content	1	2	3	4
17. I am worried	1	2	3	4
18. I feel confused	1	2	3	4
19. I feel steady	1	2	3	4
20. I feel pleasant	1	2	3	4

SELF-EVALUATION QUESTIONNAIRE

STAI Form Y-2

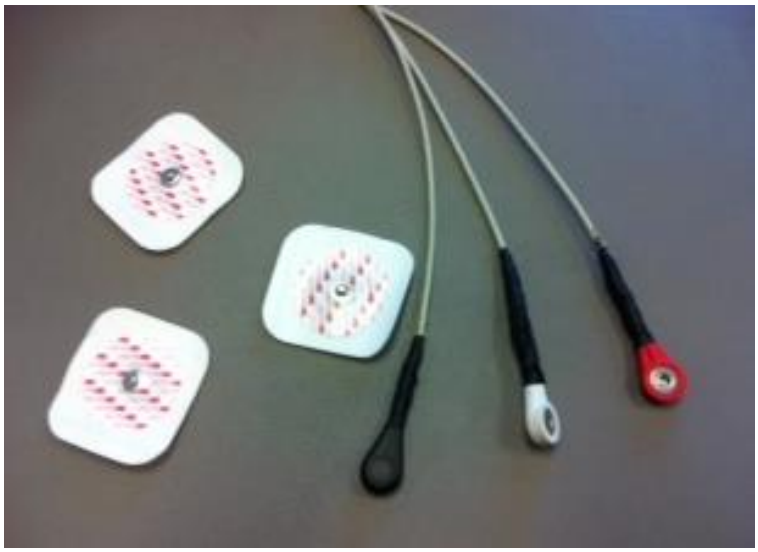
Name_____Date_____

DIRECTIONS

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you *generally* feel.

	ALMOST NEVER	SOMETIMES	OFTEN	ALMOST ALWAYS
21. I feel pleasant	1	2	3	4
22. I feel nervous and restless	1	2	3	4
23. I feel satisfied with myself	1	2	3	4
24. I wish I could be as happy as others seem to be	1	2	3	4
25. I feel like a failure	1	2	3	4
26. I feel rested	1	2	3	4
27. I am "calm, cool, and collected"	1	2	3	4
28. I feel that difficulties are piling up so that I cannot overcome them	1	2	3	4
29. I worry too much over something that really doesn't matter	1	2	3	4
30. I am happy	1	2	3	4
31. I have disturbing thoughts	1	2	3	4
32. I lack self-confidence	1	2	3	4
33. I feel secure	1	2	3	4
34. I make decisions easily	1	2	3	4
35. I feel inadequate	1	2	3	4
36. I am content	1	2	3	4
37. Some unimportant thought runs through my mind and bothers me	1	2	3	4
38. I take disappointments so keenly that I can't put them out of my mind	1	2	3	4
39. I am a steady person	1	2	3	4
40. I get in a state of tension or turmoil as I think over my recent concerns and interests	1	2	3	4

Appendix J: ECG Leads and Electrodes



AD Instruments, Colorado Springs, Colorado, USA

Appendix K: Data Acquisition System

Powerlab ML 870/P, AD Instruments, Colorado Springs, Colorado, USA

Appendix L: Isometric Handgrip

ZonaPLUS, Zona HEALTH, Boise, Idaho, USA

Appendix M: 24 Hour Ambulatory BP Device

SpaceLabs Inc., Redmond, Washington, USA

Appendix N: Diet and Activity Journal

Ambulatory Blood Pressure: Diet and Activity Journal

Participant code: _____

Date: _____

During the 24 hours your blood pressure is being monitored, please complete the tables below based on your diet and activity during this time.

ACTIVITY LOG

Examples of activities include: sleeping, walking, gardening, watching television, exercising, working etc.

Time	Activity
12:00am	
1:00am	
2:00am	
3:00am	
4:00am	
5:00am	
6:00am	
7:00am	
8:00am	
9:00am	
10:00am	
11:00am	
12:00pm	
1:00pm	
2:00pm	
3:00pm	
4:00pm	
5:00pm	
6:00pm	
7:00pm	
8:00pm	
9:00pm	
10:00pm	
11:00pm	

FOOD JOURNAL
Day (circle one): 1 2 3
Day of Week: _____
Please circle which of the following best describes you food intake for this day:
1) Typical 2) More than usual 3) Less than usual

Please list any vitamin, mineral or herbal supplements taken (brand, frequency & dose):
_____

Time	Location (ex. home, cafe)	All Food and Drink (including water)	Type/Preparation	Amount Eaten

Day (circle one): 1 2 3
Day of Week: _____
Please circle which of the following best describes you food intake for this day:
1) Typical 2) More than usual 3) Less than usual

Please list any vitamin, mineral or herbal supplements taken (brand, frequency & dose):
_____

Time	Location (ex. home, cafe)	All Food and Drink (including water)	Type/Preparation	Amount Eaten

Day (circle one): 1 2 3
Day of Week: _____
Please circle which of the following best describes you food intake for this day:
1) Typical 2) More than usual 3) Less than usual

Please list any vitamin, mineral or herbal supplements taken (brand, frequency & dose):
_____

Time	Location (ex. home, cafe)	All Food and Drink (including water)	Type/Preparation	Amount Eaten

Appendix O: Exercise Log

Participant ID: _____

Date	What was your maximum contraction value? $Right_{max}$ $Left_{max}$	Did you complete two sets with each hand? (% at end of session)	Have you had any new medications prescribed to you and/or have you started to take any new over the counter products?	Have you had any dietary changes? If yes, please describe.	Have you had any physical activity changes? If yes, please describe.

Appendix P: Raw Data for Chapter 2

Participant Characteristics

ID #	Group	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)
1	Young	19	171	64	22
2	Young	23	183	80	24
3	Young	21	165	50	18
4	Young	21	171	64	22
5	Young	22	174	59	20
6	Young	23	152	49	21
7	Young	23	165	68	25
8	Older	67	160	77	30
9	Older	70	163	59	22
10	Older	59	157	51	21
11	Older	69	168	93	33
12	Older	65	168	70	25
13	Older	54	155	61	25
14	Older	54	163	68	26

Resting Systolic Blood Pressure Data

ID #	Group	Pre-IHG Training SBP (mmHg)	Post-IHG Training SBP (mmHg)
1	Young	105	103
2	Young	109	103
3	Young	99	101
4	Young	102	99
5	Young	97	94
6	Young	102	97
7	Young	104	101
8	Older	135	122
9	Older	104	99
10	Older	116	89
11	Older	104	103
12	Older	92	103
13	Older	107	99
14	Older	111	105

Resting Diastolic Blood Pressure Data

ID #	Group	Pre-IHG Training DBP (mmHg)	Post-IHG Training DBP (mmHg)
1	Young	63	66
2	Young	76	66
3	Young	60	71
4	Young	60	59
5	Young	60	58
6	Young	59	54
7	Young	56	55
8	Older	74	64
9	Older	59	60
10	Older	73	64
11	Older	63	61
12	Older	48	56
13	Older	57	59
14	Older	65	59

Resting Heart Rate Data

ID #	Group	Pre-IHG Training HR (beats/minute)	Post-IHG Training HR (beats/minute)
1	Young	77	83
2	Young	65	59
3	Young	74	67
4	Young	86	85
5	Young	75	68
6	Young	56	50
7	Young	64	64
8	Older	62	65
9	Older	73	76
10	Older	59	70
11	Older	65	66
12	Older	73	73
13	Older	56	62
14	Older	74	68

Resting Mean Arterial Pressure Data

ID #	Group	Pre-IHG Training MAP (mmHg)	Post-IHG Training MAP (mmHg)
1	Young	77	78
2	Young	87	78
3	Young	73	81
4	Young	74	72
5	Young	72	70
6	Young	73	68
7	Young	72	70
8	Older	94	83
9	Older	74	73
10	Older	87	72
11	Older	77	75
12	Older	63	72
13	Older	74	72
14	Older	80	74

Resting Pulse Pressure Data

ID #	Group	Pre-IHG Training PP (mmHg)	Post-IHG Training PP (mmHg)
1	Young	42	37
2	Young	33	37
3	Young	39	30
4	Young	42	40
5	Young	37	36
6	Young	43	43
7	Young	48	46
8	Older	61	58
9	Older	45	39
10	Older	43	25
11	Older	41	42
12	Older	44	47
13	Older	50	40
14	Older	46	46

Ambulatory Systolic Blood Pressure Data

ID #	Group	Pre-IHG Training 24 hour ASBP (mmHg)	Post-IHG Training 24 hour ASBP (mmHg)	Pre-IHG Training Daytime ASBP (mmHg)	Post-IHG Training Daytime ASBP (mmHg)	Pre-IHG Training Nighttime ASBP (mmHg)	Post-IHG Training Nighttime ASBP (mmHg)
1	Young	120	120	119	120	120	120
2	Young	127	117	129	118	123	113
3	Young	121	119	129	122	107	114
4	Young	117	115	118	115	115	115
5	Young	113	110	117	114	106	103
6	Young	119	111	121	113	114	105
7	Young	122	122	125	122	118	115
8	Older	138	133	141	133	131	133
9	Older	122	110	127	118	115	94
10	Older	97	95	100	96	91	94
11	Older	120	107	125	108	109	106
12	Older	107	-	108	-	105	-
13	Older	119	113	124	117	111	106
14	Older	116	-	-	-	-	-

Ambulatory Diastolic Blood Pressure Data

ID #	Group	Pre-IHG Training 24 hour ADBP (mmHg)	Post-IHG Training 24 hour ADBP (mmHg)	Pre-IHG Training Daytime ADBP (mmHg)	Post-IHG Training Daytime ADBP (mmHg)	Pre-IHG Training Nighttime ADBP (mmHg)	Post-IHG Training Nighttime ADBP (mmHg)
1	Young	68	68	67	69	70	67
2	Young	80	69	81	71	77	64
3	Young	75	72	82	77	63	63
4	Young	65	65	68	63	59	69
5	Young	63	66	68	72	56	55
6	Young	67	65	68	68	65	59
7	Young	70	69	74	72	62	63
8	Older	78	76	80	77	73	73
9	Older	76	67	79	73	70	55
10	Older	59	62	61	64	53	59
11	Older	70	62	73	65	62	59
12	Older	68	-	69	-	65	-
13	Older	65	63	67	66	59	56
14	Older	70	-	-	-	-	-

Ambulatory Heart Rate Data

ID #	Group	Pre-IHG Training 24 hour AHR (beats/min)	Post-IHG Training 24 hour AHR (beats/min)	Pre-IHG Training Daytime AHR (beats/min)	Post-IHG Training Daytime AHR (beats/min)	Pre-IHG Training Nighttime AHR (beats/min)	Post-IHG Training Nighttime AHR (beats/min)
1	Young	78	73	77	76	80	66
2	Young	66	68	71	69	56	67
3	Young	87	83	91	85	80	80
4	Young	81	86	84	83	75	92
5	Young	78	81	80	82	75	78
6	Young	57	52	58	54	56	48
7	Young	67	67	68	68	67	65
8	Older	68	79	68	79	69	79
9	Older	77	76	80	78	72	71
10	Older	65	70	67	72	61	64
11	Older	73	74	73	77	71	69
12	Older	82	-	85	-	77	-
13	Older	64	61	66	62	59	57
14	Older	72	-	-	-	-	-

Serial Subtraction Task Systolic Blood Pressure Reactivity Data

ID #	Group	Pre-IHG Training SBP Reactivity (ΔmmHg)	Post-IHG Training SBP Reactivity (ΔmmHg)
1	Young	7	9
2	Young	13	7
3	Young	13	11
4	Young	7	8
5	Young	5	3
6	Young	19	15
7	Young	8	10
8	Older	8	12
9	Older	29	26
10	Older	12	-
11	Older	14	15
12	Older	23	12
13	Older	30	14
14	Older	13	16

Serial Subtraction Task Diastolic Blood Pressure Reactivity Data

ID #	Group	Pre-IHG Training DBP Reactivity (ΔmmHg)	Post-IHG Training DBP Reactivity (ΔmmHg)
1	Young	5	2
2	Young	6	2
3	Young	18	17
4	Young	8	9
5	Young	5	7
6	Young	9	10
7	Young	6	5
8	Older	2	16
9	Older	14	10
10	Older	5	-
11	Older	8	14
12	Older	20	10
13	Older	11	10
14	Older	7	2

Serial Subtraction Task Heart Rate Reactivity Data

ID #	Group	Pre-IHG Training HR Reactivity (Δbeats/minute)	Post-IHG Training HR Reactivity (Δbeats/minute)
1	Young	10	8
2	Young	1	4
3	Young	8	11
4	Young	10	13
5	Young	7	12
6	Young	14	13
7	Young	9	11
8	Older	5	4
9	Older	14	11
10	Older	9	-
11	Older	5	8
12	Older	6	1
13	Older	10	9
14	Older	2	2

Isometric Handgrip Task Systolic Blood Pressure Reactivity Data

ID #	Group	Pre-IHG Training SBP Reactivity (ΔmmHg)	Post-IHG Training SBP Reactivity (ΔmmHg)
1	Young	6	18
2	Young	11	15
3	Young	13	11
4	Young	10	13
5	Young	10	9
6	Young	13	15
7	Young	10	10
8	Older	1	6
9	Older	16	25
10	Older	5	8
11	Older	20	8
12	Older	15	8
13	Older	11	16
14	Older	11	22

Isometric Handgrip Task Diastolic Blood Pressure Reactivity Data

ID #	Group	Pre-IHG Training DBP Reactivity (ΔmmHg)	Post-IHG Training DBP Reactivity (ΔmmHg)
1	Young	7	6
2	Young	6	4
3	Young	17	16
4	Young	12	11
5	Young	5	5
6	Young	8	14
7	Young	11	13
8	Older	1	6
9	Older	5	8
10	Older	6	1
11	Older	6	7
12	Older	12	7
13	Older	2	2
14	Older	4	2

Isometric Handgrip Task Heart Rate Reactivity Data

ID #	Group	Pre-IHG Training HR Reactivity (Δbeats/minute)	Post-IHG Training HR Reactivity (Δbeats/minute)
1	Young	5	15
2	Young	2	10
3	Young	16	12
4	Young	10	11
5	Young	2	5
6	Young	10	8
7	Young	12	14
8	Older	3	5
9	Older	7	6
10	Older	10	6
11	Older	4	2
12	Older	4	3
13	Older	1	6
14	Older	0	0

Appendix Q: Statistical Data for Chapter 2

Participant Baseline Characteristics

One-Way ANOVA: Baseline Age Between-Group Differences

1a. Age (Means)

Group	Mean	Standard Deviation	n
Young	21.71	1.50	7
Older	62.57	6.85	7

1b. Age (All Effects)

ANOVA

Age

	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	5842.571	1	5842.571	237.549	.000
Within Groups	295.143	12	24.595		
Total	6137.714	13			

One-Way ANOVA: Baseline Height Between-Group Differences

2a. Height (Means)

Group	Mean	Standard Deviation	n
Young	168.71	9.57	7
Older	162.00	5.03	7

2b. Height (All Effects)

ANOVA

Height

	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	157.786	1	157.786	2.699	.126
Within Groups	701.429	12	58.452		
Total	859.214	13			

One-Way ANOVA: Baseline Weight Between-Group Differences

3a. Weight (Means)

Group	Mean	Standard Deviation	n
Young	62.00	10.72	7
Older	68.43	13.71	7

3b. Weight (All Effects)

ANOVA

Weight

	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	144.643	1	144.643	.955	.348
Within Groups	1817.714	12	151.476		
Total	1962.357	13			

One-Way ANOVA: Baseline BMI Between-Group Differences

4a. BMI (Means)

Group	Mean	Standard Deviation	n
Young	21.71	2.36	7
Older	26.00	4.24	7

4b. BMI (All Effects)

ANOVA

BMI

	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	64.286	1	64.286	5.455	.038
Within Groups	141.429	12	11.786		
Total	205.714	13			

One-Way ANOVA: Baseline Resting BP and HR Between-Group Differences

5a. Resting SBP (Means)

Group	Mean	Standard Deviation	n
Young	102.57	3.95	7
Older	109.86	13.34	7

5b. Resting SBP (All Effects)

ANOVA

RestingSBP

	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	185.786	1	185.786	1.921	.191
Within Groups	1160.571	12	96.714		
Total	1346.357	13			

6a. Resting DBP (Means)

Group	Mean	Standard Deviation	n
Young	62.00	6.51	7
Older	62.71	9.14	7

6b. Resting DBP (All Effects)

ANOVA

RestingDBP

	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	1.786	1	1.786	.028	.869
Within Groups	755.429	12	62.952		
Total	757.214	13			

7a. Resting HR (Means)

Group	Mean	Standard Deviation	n
Young	71.00	9.97	7
Older	66.00	7.39	7

7b. Resting HR (All Effects)

ANOVA

RestingHR

	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	87.500	1	87.500	1.136	.307
Within Groups	924.000	12	77.000		
Total	1011.500	13			

8a. Resting MAP (Means)

Group	Mean	Standard Deviation	n
Young	75.43	5.38	7
Older	78.43	9.98	7

8b. Resting MAP (All Effects)

ANOVA

RestingMAP

	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	31.500	1	31.500	.490	.497
Within Groups	771.429	12	64.286		
Total	802.929	13			

9a. Resting PP (Means)

Group	Mean	Standard Deviation	n
Young	40.57	4.79	7
Older	47.14	6.71	7

9b. Resting PP (All Effects)

ANOVA

RestingPP

	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	151.143	1	151.143	4.439	.057
Within Groups	408.571	12	34.048		
Total	559.714	13			

One-Way ANOVA: Baseline Ambulatory BP and HR Between-Group Differences

10a. 24 Hour Ambulatory SBP (Means)

Group	Mean	Standard Deviation	n
Young	119.86	4.34	7
Older	119.20	14.62	5

10b. 24 Hour Ambulatory SBP (All Effects)

ANOVA

FullASBP

	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	1.260	1	1.260	.013	.911
Within Groups	967.657	10	96.766		
Total	968.917	11			

11a. Daytime Ambulatory SBP (Means)

Group	Mean	Standard Deviation	n
Young	122.57	5.09	7
Older	123.40	14.78	5

11b. Daytime Ambulatory SBP (All Effects)

ANOVA

DayASBP

	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	2.002	1	2.002	.019	.892
Within Groups	1028.914	10	102.891		
Total	1030.917	11			

12a. Nighttime Ambulatory SBP (Means)

Group	Mean	Standard Deviation	n
Young	114.71	6.37	7
Older	111.40	14.31	5

12b. Nighttime Ambulatory SBP (All Effects)

ANOVA

NightASBP

	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	32.038	1	32.038	.301	.595
Within Groups	1062.629	10	106.263		
Total	1094.667	11			

13a. 24 Hour Ambulatory DBP (Means)

Group	Mean	Standard Deviation	n
Young	69.71	5.94	7
Older	69.60	7.83	5

13b. 24 Hour Ambulatory DBP (All Effects)

ANOVA

FullADBP

	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	.038	1	.038	.001	.978
Within Groups	456.629	10	45.663		
Total	456.667	11			

14a. Daytime Ambulatory DBP (Means)

Group	Mean	Standard Deviation	n
Young	72.57	6.53	7
Older	72.00	8.06	5

14b. Daytime Ambulatory DBP (All Effects)

ANOVA

DayADBP

	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	.952	1	.952	.018	.895
Within Groups	515.714	10	51.571		
Total	516.667	11			

15a. Nighttime Ambulatory DBP (Means)

Group	Mean	Standard Deviation	n
Young	64.57	7.04	7
Older	63.40	8.14	5

15b. Nighttime Ambulatory DBP (All Effects)

ANOVA

NightADBP

	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	4.002	1	4.002	.071	.795
Within Groups	562.914	10	56.291		
Total	566.917	11			

16a. 24 Hour Ambulatory HR (Means)

Group	Mean	Standard Deviation	n
Young	73.43	10.41	7
Older	69.40	5.51	5

16b. 24 Hour Ambulatory HR (All Effects)

ANOVA

FullAHR

	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	47.336	1	47.336	.614	.451
Within Groups	770.914	10	77.091		
Total	818.250	11			

17a. Daytime Ambulatory HR (Means)

Group	Mean	Standard Deviation	n
Young	75.57	10.94	7
Older	70.80	5.81	5

17b. Daytime Ambulatory HR (All Effects)

ANOVA

DayAHR

	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	66.402	1	66.402	.779	.398
Within Groups	852.514	10	85.251		
Total	918.917	11			

18a. Nighttime Ambulatory HR (Means)

Group	Mean	Standard Deviation	n
Young	69.86	10.42	7
Older	66.40	5.98	5

18b. Nighttime Ambulatory HR (All Effects)

ANOVA

NightAHR

	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	34.860	1	34.860	.439	.523
Within Groups	794.057	10	79.406		
Total	828.917	11			

Effects of IHG Training on Resting and Ambulatory BP and HR

Resting BP and HR Pre- to Post-IHG Training Repeated Measures ANOVA

1a. Resting SBP (Means)

Group	Time	Mean	Standard Deviation	n
Young	Pre-Training	102.57	3.95	7
Young	Post-Training	99.71	3.30	7
Older	Pre-Training	109.86	13.34	7
Older	Post-Training	102.86	9.94	7

1b. Resting SBP (All Effects)

Tests of Within-Subjects Contrasts

Measure: RestingSBP

Source	Time	Type III Sum of Squares	Df	Mean Square	F	Sig.
Time	Linear	170.036	1	170.036	4.853	.048
Time * Group	Linear	30.036	1	30.036	.857	.373
Error(Time)	Linear	420.429	12	35.036		

2a. Resting DBP (Means)

Group	Time	Mean	Standard Deviation	n
Young	Pre-Training	62.00	6.51	7
Young	Post-Training	61.29	6.42	7
Older	Pre-Training	62.71	9.14	7
Older	Post-Training	60.43	2.88	7

2b. Resting DBP (All Effects)

Tests of Within-Subjects Contrasts

Measure: RestingDBP

Source	Time	Type III Sum of Squares	Df	Mean Square	F	Sig.
Time	Linear	15.750	1	15.750	.740	.407
Time * Group	Linear	4.321	1	4.321	.203	.660
Error(Time)	Linear	255.429	12	21.286		

3a. Resting HR (Means)

Group	Time	Mean	Standard Deviation	n
Young	Pre-Training	71.00	9.97	7
Young	Post-Training	68.00	12.49	7
Older	Pre-Training	66.00	7.39	7
Older	Post-Training	68.57	4.82	7

3b. Resting HR (All Effects)

Tests of Within-Subjects Contrasts

Measure: RestingHR

Source	Time	Type III Sum of Squares	Df	Mean Square	F	Sig.
Time	Linear	.321	1	.321	.025	.877
Time * Group	Linear	54.321	1	54.321	4.209	.063
Error(Time)	Linear	154.857	12	12.905		

4a. Resting MAP (Means)

Group	Time	Mean	Standard Deviation	n
Young	Pre-Training	75.43	5.38	7
Young	Post-Training	73.86	5.05	7
Older	Pre-Training	78.43	9.98	7
Older	Post-Training	74.43	3.95	7

4b. Resting MAP (All Effects)

Tests of Within-Subjects Contrasts

Measure: RestingMAP

Source	Time	Type III Sum of Squares	Df	Mean Square	F	Sig.
Time	Linear	54.321	1	54.321	2.480	.141
Time * Group	Linear	10.321	1	10.321	.471	.505
Error(Time)	Linear	262.857	12	21.905		

5a. Resting PP (Means)

Group	Time	Mean	Standard Deviation	n
Young	Pre-Training	40.57	4.79	7
Young	Post-Training	38.43	5.19	7
Older	Pre-Training	47.14	6.72	7
Older	Post-Training	42.43	9.98	7

5b. Resting PP (All Effects)

Tests of Within-Subjects Contrasts

Measure: RestingPP

Source	Time	Type III Sum of Squares	Df	Mean Square	F	Sig.
Time	Linear	82.286	1	82.286	4.677	.051
Time * Group	Linear	11.571	1	11.571	.658	.433
Error(Time)	Linear	211.143	12	17.595		

Ambulatory BP and HR Pre- to Post-IHG Training Repeated Measures ANOVA

6a. 24 Hour Ambulatory SBP (Means)

Group	Time	Mean	Standard Deviation	n
Young	Pre-Training	119.86	4.34	7
Young	Post-Training	116.29	4.54	7
Older	Pre-Training	119.2	14.62	5
Older	Post-Training	111.6	13.78	5

6b. 24 Hour Ambulatory SBP (All Effects)

Tests of Within-Subjects Contrasts

Measure: FullSBP

Source	Time	Type III Sum of Squares	Df	Mean Square	F	Sig.
Time	Linear	182.001	1	182.001	20.120	.001
Time * Group	Linear	23.668	1	23.668	2.616	.137
Error(Time)	Linear	90.457	10	9.046		

7a. Daytime Ambulatory SBP (Means)

Group	Time	Mean	Standard Deviation	n
Young	Pre-Training	122.57	5.09	7
Young	Post-Training	117.71	3.77	7
Older	Pre-Training	123.40	14.78	5
Older	Post-Training	114.40	13.65	5

7b. Daytime Ambulatory SBP (All Effects)

Tests of Within-Subjects Contrasts

Measure: DayASBP

Source	Time	Type III Sum of Squares	Df	Mean Square	F	Sig.
Time	Linear	280.030	1	280.030	29.344	.000
Time * Group	Linear	25.030	1	25.030	2.623	.136
Error(Time)	Linear	95.429	10	9.543		

8a. Nighttime Ambulatory SBP (Means)

Group	Time	Mean	Standard Deviation	n
Young	Pre-Training	114.71	6.37	7
Young	Post-Training	112.14	6.01	7
Older	Pre-Training	111.40	14.31	5
Older	Post-Training	106.60	15.93	5

8b. Nighttime Ambulatory SBP (All Effects)

Tests of Within-Subjects Contrasts

Measure: NightASBP

Source	Time	Type III Sum of Squares	Df	Mean Square	F	Sig.
Time	Linear	79.243	1	79.243	2.759	.128
Time * Group	Linear	7.243	1	7.243	.252	.626
Error(Time)	Linear	287.257	10	28.726		

9a. 24 Hour Ambulatory DBP (Means)

Group	Time	Mean	Standard Deviation	n
Young	Pre-Training	69.71	5.94	7
Young	Post-Training	67.71	2.56	7
Older	Pre-Training	69.60	7.83	5
Older	Post-Training	66.00	5.96	5

9b. 24 Hour Ambulatory DBP (All Effects)

Tests of Within-Subjects Contrasts

Measure: FullADBP

Source	Time	Type III Sum of Squares	Df	Mean Square	F	Sig.
Time	Linear	45.733	1	45.733	4.290	.065
Time * Group	Linear	3.733	1	3.733	.350	.567
Error(Time)	Linear	106.600	10	10.660		

10a. Daytime Ambulatory DBP (Means)

Group	Time	Mean	Standard Deviation	n
Young	Pre-Training	72.57	6.53	7
Young	Post-Training	70.29	4.31	7
Older	Pre-Training	72.00	8.06	5
Older	Post-Training	69.00	5.70	5

10b. Daytime Ambulatory DBP (All Effects)

Tests of Within-Subjects Contrasts

Measure: DayADBP

Source	Time	Type III Sum of Squares	Df	Mean Square	F	Sig.
Time	Linear	40.744	1	40.744	3.854	.078
Time * Group	Linear	.744	1	.744	.070	.796
Error(Time)	Linear	105.714	10	10.571		

11a. Nighttime Ambulatory DBP (Means)

Group	Time	Mean	Standard Deviation	n
Young	Pre-Training	64.57	7.04	7
Young	Post-Training	62.86	4.71	7
Older	Pre-Training	63.40	8.14	5
Older	Post-Training	60.40	7.27	5

11b. Nighttime Ambulatory DBP (All Effects)

Tests of Within-Subjects Contrasts

Measure: NightADBP

Source	Time	Type III Sum of Squares	Df	Mean Square	F	Sig.
Time	Linear	32.411	1	32.411	1.224	.294
Time * Group	Linear	2.411	1	2.411	.091	.769
Error(Time)	Linear	264.714	10	26.471		

12a. 24Hour Ambulatory HR (Means)

Group	Time	Mean	Standard Deviation	n
Young	Pre-Training	73.43	10.41	7
Young	Post-Training	72.86	11.80	7
Older	Pre-Training	69.40	5.51	5
Older	Post-Training	72.00	6.96	5

12b. 24 Hour Ambulatory HR (All Effects)

Tests of Within-Subjects Contrasts

Measure: FullAHR

Source	Time	Type III Sum of Squares	Df	Mean Square	F	Sig.
Time	Linear	6.001	1	6.001	.534	.482
Time * Group	Linear	14.668	1	14.668	1.304	.280
Error(Time)	Linear	112.457	10	11.246		

13a. Daytime Ambulatory HR (Means)

Group	Time	Mean	Standard Deviation	n
Young	Pre-Training	75.57	10.94	7
Young	Post-Training	73.86	11.04	7
Older	Pre-Training	70.80	5.81	5
Older	Post-Training	73.60	7.02	5

13b. Daytime Ambulatory HR (All Effects)

Tests of Within-Subjects Contrasts

Measure: DayAHR

Source	Time	Type III Sum of Squares	Df	Mean Square	F	Sig.
Time	Linear	1.719	1	1.719	.187	.675
Time * Group	Linear	29.719	1	29.719	3.226	.103
Error(Time)	Linear	92.114	10	9.211		

14a. Nighttime Ambulatory HR (Means)

Group	Time	Mean	Standard Deviation	n
Young	Pre-Training	69.86	10.42	7
Young	Post-Training	70.86	14.00	7
Older	Pre-Training	66.40	5.98	5
Older	Post-Training	68.00	8.19	5

14b. Nighttime Ambulatory HR (All Effects)

Tests of Within-Subjects Contrasts

Measure: NightAHR

Source	Time	Type III Sum of Squares	Df	Mean Square	F	Sig.
Time	Linear	9.858	1	9.858	.252	.626
Time * Group	Linear	.525	1	.525	.013	.910
Error(Time)	Linear	390.600	10	39.060		

Cardiovascular Reactivity as a Predictor of IHG Training Effectiveness in Young and Older Women

1a. Correlation Analysis (Young)

Marked correlations are significant at P <0.05, n=7.						
RSBP	SST SBP	SST DBP	SST HR	IHGT SBP	IHGT DBP	IHGT HR
	r= -0.114	r= 0.610	r= -0.059	r= -0.135	r= 0.719	r= 0.556
	p= 0.808	p= 0.146	p= 0.901	p= 0.773	p= 0.069	p= 0.195
RSBP, Resting systolic blood pressure						

Marked correlations are significant at P <0.05, n=7.						
ASBP	SST SBP	SST DBP	SST HR	IHGT SBP	IHGT DBP	IHGT HR
	r= -0.566	r= 0.090	r= 0.155	r= -0.522	r= 0.474	r= 0.425
	p= 0.185	p= 0.847	p= 0.740	p= 0.230	p= 0.282	p= 0.342
ASBP, 24 hour ambulatory systolic blood pressure						

Marked correlations are significant at P <0.05, n=7.						
DASBP	SST SBP	SST DBP	SST HR	IHGT SBP	IHGT DBP	IHGT HR
	r= -0.583	r= -0.003	r= 0.085	r= -0.633	r= 0.320	r= 0.268
	p= 0.169	p= 0.994	p= 0.857	p= 0.127	p= 0.485	p= 0.562
DASBP, Daytime ambulatory systolic blood pressure						

1b. Correlation Analysis (Older)

Marked correlations are significant at P <0.05, n=7.						
RSBP	SST SBP	SST DBP	SST HR	IHGT SBP	IHGT DBP	IHGT HR
	r= -0.053	r= 0.211	r= -0.450	r= 0.158	r= 0.043	r= -0.638
	p= 0.911	p= 0.650	p= 0.311	p= 0.736	p= 0.927	p= 0.123
RSBP, Resting systolic blood pressure						

Marked correlations are significant at P <0.05, n=5.						
ASBP	SST SBP	SST DBP	SST HR	IHGT SBP	IHGT DBP	IHGT HR
	r= -0.388	r= -0.678	r= -0.240	**r= -0.968**	r= -0.608	r= -0.039
	p= 0.518	p= 0.208	p= 0.697	p= 0.007	p= 0.277	p= 0.950
ASBP, 24 hour ambulatory systolic blood pressure						

Marked correlations are significant at P <0.05, n=5.						
DASBP	SST SBP	SST DBP	SST HR	IHGT SBP	IHGT DBP	IHGT HR
	r= 0.091	r= -0.195	r= 0.334	r= -0.810	r= -0.595	r= 0.064
	p= 0.884	p= 0.753	p= 0.582	p= 0.097	p= 0.290	p= 0.918
DASBP, Daytime ambulatory systolic blood pressure						

Cardiovascular Reactivity Post-IHG Training

SST Systolic BP, Diastolic BP, and HR Reactivity Pre- to Post-IHG Training Repeated Measures ANOVA

1a. SST Systolic BP Reactivity (Means)

Group	Time	Mean	Standard Deviation	n
Young	Pre-Training	10.29	4.92	7
Young	Post-Training	9.00	3.70	7
Older	Pre-Training	18.43	8.81	7
Older	Post-Training	15.83	5.23	6

1b. SST Systolic BP Reactivity (All Effects)

Tests of Within-Subjects Contrasts

Measure: SST_SBP_Reactivity

Source	Time	Type III Sum of Squares	df	Mean Square	F	Sig.
Time	Linear	39.619	1	39.619	2.242	.162
Time * Group	Linear	9.158	1	9.158	.518	.487
Error(Time)	Linear	194.381	11	17.671		

2a. SST Diastolic BP Reactivity (Means)

Group	Time	Mean	Standard Deviation	n
Young	Pre-Training	8.14	4.60	7
Young	Post-Training	7.43	5.26	7
Older	Pre-Training	9.57	6.02	7
Older	Post-Training	10.33	4.80	6

2b. SST Diastolic BP Reactivity (All Effects)

Tests of Within-Subjects Contrasts

Measure: SST_DBP_Reactivity

Source	Time	Type III Sum of Squares	df	Mean Square	F	Sig.
Time	Linear	.824	1	.824	.045	.836
Time * Group	Linear	.824	1	.824	.045	.836
Error(Time)	Linear	201.714	11	18.338		

3a. SST HR Reactivity (Means)

Group	Time	Mean	Standard Deviation	n
Young	Pre-Training	8.43	3.95	7
Young	Post-Training	10.29	3.25	7
Older	Pre-Training	7.29	3.99	7
Older	Post-Training	5.83	4.07	6

3b. SST HR Reactivity (All Effects)

Tests of Within-Subjects Contrasts

Measure: SST_HR_Reactivity

Source	Time	Type III Sum of Squares	df	Mean Square	F	Sig.
Time	Linear	.770	1	.770	.230	.641
Time * Group	Linear	14.770	1	14.770	4.410	.060
Error(Time)	Linear	36.845	11	3.350		

IHGT Systolic BP, Diastolic BP, and HR Reactivity Pre- to Post-IHG Training Repeated Measures ANOVA

4a. IHGT Systolic BP Reactivity (Means)

Group	Time	Mean	Standard Deviation	n
Young	Pre-Training	10.43	2.37	7
Young	Post-Training	13.00	3.21	7
Older	Pre-Training	11.29	6.55	7
Older	Post-Training	13.29	7.72	7

4b. IHGT Systolic BP Reactivity (All Effects)

Tests of Within-Subjects Contrasts

Measure: IHGT_SBP_Reactivity

Source	Time	Type III Sum of Squares	df	Mean Square	F	Sig.
Time	Linear	36.571	1	36.571	1.574	.234
Time * Group	Linear	.571	1	.571	.025	.878
Error(Time)	Linear	278.857	12	23.238		

5a. IHGT Diastolic BP Reactivity (Means)

Group	Time	Mean	Standard Deviation	n
Young	Pre-Training	9.43	4.20	7
Young	Post-Training	9.86	4.81	7
Older	Pre-Training	5.14	3.58	7
Older	Post-Training	4.71	2.93	7

5b. IHGT Diastolic BP Reactivity (All Effects)

Tests of Within-Subjects Contrasts

Measure: IHGT_DBP_Reactivity

Source	Time	Type III Sum of Squares	df	Mean Square	F	Sig.
Time	Linear	.000	1	.000	.000	1.000
Time * Group	Linear	1.286	1	1.286	.231	.639
Error(Time)	Linear	66.714	12	5.560		

6a. IHGT HR Reactivity (Means)

Group	Time	Mean	Standard Deviation	n
Young	Pre-Training	8.14	5.30	7
Young	Post-Training	10.71	3.45	7
Older	Pre-Training	4.14	3.44	7
Older	Post-Training	4.00	2.38	7

6b. IHGT HR Reactivity (All Effects)

Tests of Within-Subjects Contrasts

Measure: IHGT_HR_Reactivity

Source	Time	Type III Sum of Squares	Df	Mean Square	F	Sig.
Time	Linear	10.321	1	10.321	1.223	.290
Time * Group	Linear	12.893	1	12.893	1.528	.240
Error(Time)	Linear	101.286	12	8.440		

Vita Auctoris

Mary Ann Zokvic was born in 1992 in Windsor, Ontario to Nevenka and Dragutin Zokvic. Mary Ann completed her high school education at St. Anne's High School in Windsor, Ontario in the year 2010. She then went on to earn a Bachelor of Science in Behaviour, Cognition and Neuroscience at the University of Windsor in 2014. It was during her undergraduate degree that Mary Ann completed an undergraduate thesis which led to her introduction to the Faculty of Human Kinetics and subsequent achievement of a Master of Human Kinetics degree at the University of Windsor in 2017 under the supervision of Drs. Cheri McGowan and Kevin Milne. Utilizing everything she has gained from her experience at the University of Windsor, Mary Ann is pursuing a career in medicine at the University of Toronto this fall.