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Application of Isometric Resistance Training to Treat Hypertension

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Abstract

The objective of this thesis was to test the hypotheses that in medicated, borderline-Stage 1 hypertensive individuals, 8 weeks of isometric handgrip (IHG) training (3X/week) would elicit reductions in resting and ambulatory blood pressure (BP), and that these reductions would be predicted by cardiovascular reactivity to an IHG task (a 2-minute sustained isometric contraction). Additionally, it was hypothesized that 4 weeks of detraining following 8 weeks of IHG training would lead to BP returning to baseline values. Cardiovascular reactivity to an IHG task was determined prior to IHG training, while resting BP and ambulatory BP were determined prior to and following 8 weeks of IHG training, and again after 4 weeks of no training (n = 4; resting BP: 134/77 ± 14/10 mmHg; age: 58 ± 2 years). IHG training did not elicit statistically significant reductions in BP ($P > 0.05$), and BP did not change following 4 weeks of detraining. Pre-IHG training cardiovascular reactivity to the IHG task was not strongly correlated to IHG training-induced changes in resting or ambulatory BP.

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List of Abbreviations

ACE	Angiotensin Converting Enzyme
AOBP	Automated Office Blood Pressure
ANP	Atrial Natriuretic Peptide
ANS	Autonomic Nervous System
ARs	Adrenergic Receptors
ATP	Adenosine Triphosphate
BP	Blood Pressure
Ca^{2+}	Calcium
CC	Central Command
CCC	Cardiovascular Control Center
CVD	Cardiovascular Disease
DASH	Dietary Approach to Stop Hypertension
DBP	Diastolic Blood Pressure
E	Epinephrine
EMG	Electromyography
EPR	Exercise Pressor Reflex
ET-1	Endothelin-1
FMD	Flow-Mediated Dilation
IHG	Isometric Handgrip
IL	Isometric Leg
IRT	Isometric Resistance Training
$[H^+]$	Hydrogen Ion Concentration

HR	Heart Rate
HRV	Heart Rate Variability
HTN	Hypertension
K^+	Potassium
MAP	Mean Arterial Blood Pressure
mmHg	Millimeters of Mercury
MVC	Maximum Voluntary Contraction
NE	Norepinephrine
NO	Nitric Oxide
$PaCO_2$	Partial Pressure of Carbon Dioxide
PaO_2	Partial Pressure of Oxygen
PEH	Post-Exercise Hypotension
PNS	Parasympathetic Nervous System
Q	Cardiac Output
RAAS	Renin Angiotensin Aldosterone System
RHTN	Resistant Hypertension
SBP	Systolic Blood Pressure
SNS	Sympathetic Nervous System
SV	Stroke Volume
TPR	Total Peripheral Resistance

Chapter 1: Literature Review

1.1 Cardiovascular Disease

Cardiovascular disease (CVD) encompasses all disorders of the heart and circulatory system that interfere with efficient functioning (Go et al, 2014). CVD includes conditions such as coronary heart disease, cerebrovascular disease, elevated blood pressure (BP) or hypertension (HTN), rheumatic heart disease and heart failure, and is the leading cause of death globally, as well as in Canada (Statistics Canada, 2015a; WHO, 2017). Locally, CVD represented 35% of all causes of death between 2005-2007 in Windsor-Essex County, and the rate of mortality from CVD was 25% higher in Windsor-Essex County in comparison to the province of Ontario (Statistics Canada, 2013). The medical costs of CVD in Canada amount to more than $20.9 billion per annum and are expected to rise to a total of $28.3 billion by the year 2020 (Conference Board of Canada, 2010). Accordingly, the WHO considers the early prevention and treatment of CVD of the utmost importance (WHO, 2017). Realizing the potential in prevention, the Ontario government has created initiatives such as the Heart Health Program, one of the largest CVD prevention programs in North America that raises awareness of key lifestyle factors, such as diet, tobacco use, and exercise, which have been shown to alter the risk of CVD (Ontario Ministry of Health, 2012).

HTN is a leading modifiable risk factor for CVD, and has been deemed a global health crisis by the WHO (WHO, 2013). Closer to home, this is reflected by the fact that of the approximately 17 million CVD related deaths per year, 9.4 million are directly attributed to HTN (WHO, 2013). One in 5 Canadians have HTN, and in Windsor-Essex County, 27% of individuals aged 45-64 years and 48% of individuals aged 65 years and over were reported to have HTN in 2012 (Wilkins et al., 2010; Windsor-Essex County

Health Unit, 2016). With the percentage of people aged 50 years and over increasing each year in Canada, the number of individuals diagnosed with HTN will likely continue to rise (Statistics Canada, 2015b).

1.2 Hypertension

Arterial BP is composed of systolic BP (SBP) and diastolic BP (DBP), which represent different phases of the cardiac cycle (Herd, 1970). SBP represents the maximum pressure the blood is exerting against the arterial walls when the heart beats, while DBP indicates the pressure that is exerted on the arteries when the heart is relaxed between beats (American Heart Association, 2016). Mean arterial pressure (MAP) represents the average BP during a single cardiac cycle (Zheng et al., 2008). Normal values of resting SBP and DBP for adults are <120 mmHg and <80 mmHg, respectively (American Heart Association, 2016). BP that is persistently elevated above normal measures is known as HTN, which is classified by measurements of SBP ≥140 mmHg and/or DBP ≥90 mmHg (American Heart Association, 2016). However, recent evidence has shown that resting BP measures of SBP ≥135 mmHg and/or DBP ≥85 mmHg are a more accurate threshold when diagnosing HTN using an automated office blood pressure (AOBP) device (Myers et al., 2015). Using Ambulatory BP monitoring (see Section 1.2.4), individuals can be diagnosed as hypertensive if mean awake SBP is ≥135 mmHg and/or DBP is ≥85 mmHg, or if mean 24-hour SBP is ≥130 mmHg and/or DBP ≥80 mmHg (Leung et al., 2016). Individuals with pre-HTN or borderline HTN have SBP between 120-139 mmHg and/or DBP between 80-89 mmHg (Leung et al., 2016). Arterial BP within the range of 140-159/90-99 mmHg is classified as Stage 1 HTN, whereas arterial BP >160/100 mmHg is defined as Stage 2

HTN (Dosh, 2001).

HTN can be classified as either primary or secondary HTN. Primary or essential HTN represents approximately 95% of all cases of HTN, and appears to be caused by, "a complex interaction of genetics and environmental factors, including obesity, low physical activity levels, high stress levels, high alcohol consumption, high dietary sodium, and low dietary potassium" (Dosh, 2001). Secondary HTN is defined as high BP from secondary causes such as chronic renal disease, renovascular disease, or hyperaldosteronism (Dosh, 2001). There is also a difference between controlled or uncontrolled HTN. Controlled HTN is considered to be resting BP <140/90 mmHg while on medication or another form of treatment, whereas uncontrolled HTN represents a resting BP ≥140/90 mmHg (Wang & Vasan, 2005). Patients with uncontrolled HTN may be on antihypertenisve medication, have poor treatment adherence, and/or an inadequate treatment regimen (Calhoun et al., 2008). Uncontrolled HTN can be further classified as resistant HTN (RHTN), which is defined as SBP ≥140 mmHg and/or DBP ≥90 mmHg on maximally tolerated doses of three or more antihypertensive medications, one of which must be a diuretic (Calhoun et al., 2008). Most guidelines also require the need for daytime ambulatory BP monitor readings of SBP ≥135 mmHg or DBP ≥85 mmHg in order to confirm RHTN (Calhoun et al., 2008).

As noted above, HTN has been identified as a primary risk factor for the development of CVD (Lawes et al., 2008; Brook et al., 2013). HTN is a major cause of morbidity and mortality, affecting over 26.4% of adults worldwide (Kearney et al., 2005), and is responsible for 13.5% of deaths of the global population (Lawes et al.,

2008). In addition, up to 50% of individuals with HTN in Canada and the United States may have uncontrolled HTN (Wang & Vasan, 2005; Campbell et al., 2013). Due to its association with CVD related events such as coronary artery disease and stroke, the WHO deemed HTN a global health crisis and predicted an epidemic of HTN in the near future (WHO, 2013).

1.2.3 Blood Pressure Regulation

Regulation of BP is associated with the manipulation of several cardiovascular parameters, with the product of cardiac output (Q) and total peripheral resistance (TPR) representing MAP (MAP = Q x TPR) (Singh et al., 2010). Q represents the volume of blood pumped out of the heart per minute, which is the product of stroke volume (SV) and HR (Q = SV x HR) (Raven & Chapleau, 2014). TPR represents the opposition of blood flow through the systemic blood vessels (Raven & Chapleau, 2014; Charkoudian et al., 2005). Therefore, changes in BP are the result of changes in Q via increases or decreases in HR and/or SV, and in TPR via changes in arterial diameter through vasodilation or vasoconstriction of vascular smooth muscle (Singh et al., 2010). The autonomic nervous system (ANS) and endocrine reflexes are the main regulators of BP control (Gordan et al., 2015).

Autonomic Nervous System

As part of the peripheral nervous system, the ANS can regulate BP, HR, respiration rate, sweating, in addition to other autonomic functions to maintain homeostasis (Gordan et al., 2015). The ANS is composed of two interconnected systems: the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS) (Gordan et al., 2015). The effect of the ANS on BP is a constant balance between the

opposing effects of the SNS and the PNS.

The SNS prepares the body for stressful situations (known as the "fight or flight" response) (Gordan et al., 2015). Upon activation, the SNS releases norepinephrine (NE), which causes blood vessel constriction, and increased BP (Gordan et al., 2015). SNS activation also increases contractility of the heart by increasing intracellular calcium (Ca^{2+}), as well as enhancing the conductance of the electrical signals within the heart (Gordan et al., 2015). NE binds to two types of adrenergic receptors (ARs) within the SNS, known as α and β ARs (Gordan et al., 2015). Both α_1 and α_2 ARs are expressed in vascular smooth muscle and both elicit vasoconstriction upon activation, thus increasing BP (Michel et al., 1990). β_1 ARs are found in the heart and its activation elicits increased HR, myocardial contractility, and electrical conduction velocity within the heart, which leads to an increase in BP (Michel et al., 1990; Gordan et al., 2015). β_1 ARs are found throughout the body, with their activation resulting in vasodilation (increased blood perfusion) in target organs, such as the heart, liver, and skeletal muscle (Gordan et al., 2015).

Parasympathetic activity generally produces effects that oppose sympathetic activity, such as decreased HR, reduced conduction velocity through the heart, and ultimately lower BP (Gordan et al., 2015). The PNS releases acetylcholine (ACh) and is most active under resting conditions (Gordan et al., 2015). ACh binds to two types of muscarinic receptors within the PNS: the M_2 and M_3 receptors (Gordan et al., 2015). M_2 receptors are located in the heart and its activation via ACh binding reduces conduction velocity through the heart, thus reducing HR, SV, Q, and BP (Gordan et al., 2015). Activation of M_3 receptors, mainly located in vascular endothelium, cause vasodilation

by stimulating nitric oxide (NO) production from endothelial cells (Brodde & Michel, 1999; Gordan et al., 2015).

The ANS is made up several reflex arcs (Gordan et al., 2015). The central command (CC) is a control mechanism within the brain that sets the basic pattern of motor activity to skeletal muscles and drives cardiorespiratory activation by coordination with another region of the brain, the cardiovascular control centre (CCC) (Michelini et al., 2015). Activation of neural pathways within the CC modulates sympathetic and parasympathetic outflow from the CCC to change BP accordingly (Weippert et al., 2013).

Arterial baroreceptors located within the aorta and carotid sinuses are stretch receptors that detect changes in BP (Gordan et al., 2015). These stretch-sensitive baroreceptors send afferent information to the CCC to alter efferent sympathetic and parasympathetic neural output (Hart & Charkoudian, 2013). When BP is increased, these mechanoreceptors are activated via distension, and subsequently send signals to the CCC that causes sympathetic inhibition via vasodilation and parasympathetic activation (Gordan et al., 2015). This results in a decrease in TPR, HR, and Q, which returns BP back to the central set point (Gordan et al., 2015). In contrast, a reduction in BP reduces the frequency of afferent signaling from the baroreceptors to the CCC (Lafranchi & Somers, 2002). The CCC responds by withdrawing parasympathetic activity and increasing activity of sympathetic nerves (Hart & Charkoudian, 2013). This results in an increase in HR, SV, and Q, as well as an increase in TPR (vasoconstriction) to increase BP (Hart & Charkoudian, 2013).

The partial pressures of oxygen (PaO_2) and carbon dioxide ($PaCO_2$), as well as the changes in hydrogen ion concentration ($[H^+]$) are monitored by central and peripheral

chemoreceptors (O'Regan & Majcherczyk, 1982). Central chemoreceptors detect changes in $PaCO_2$ and pH within the brain, whereas peripheral chemoreceptors are located within the carotid and aortic bodies to monitor PaO_2, $PaCO_2$, and pH of the blood (Gordan et al., 2015). Both types of chemoreceptors are activated by an increase in $PaCO_2$ and/or a decrease in pH (more acidic), which increases the number of impulses to the CCC, resulting in SNS activation and PNS inhibition to increase HR, SV, Q, TPR, and BP (Gordan et al., 2015). There are also receptors involved in BP regulation within muscles. The two main muscle afferent receptors are mechanoreceptors and metaboreceptors (Leshnower et al., 2001). Mechanoreceptors are group III afferent sensory neurons that are stimulated by the physical distortion due to the pressure changes within the arterial walls during muscle contraction (Murphy et al., 2011). Metaboreceptors are group IV afferent sensory neurons that are activated by the chemical by-products of muscle contraction, such as lactate, potassium (K^+), and phosphate (Murphy et al., 2011). Mechanoreceptors are activated at the start of muscle contraction, whereas metaboreceptors are activated by the metabolites when the oxygen supply cannot meet the metabolic demands of the contracting muscle (Belli et al., 2011). Once activated, both types of receptors send impulses to the CCC, resulting in an increase in efferent sympathetic nerve activity and an inhibition of parasympathetic nerve activity in order to provide adequate oxygen and nutrient delivery to the contracting muscle (Murphy et al., 2011). Taken together, these actions result in increases in HR, SV, Q, and TPR, thus leading to an increase in BP (Murphy et al., 2011).

Endocrine Reflexes

Several endocrine hormones that are produced and released by many different

parts of the body can also regulate of BP. Epinephrine (E) is produced in the adrenal glands and initiates the fight or flight response during sympathetic activation (Gordan et al., 2015). E binds to all major ARs, eliciting vasoconstriction (increased TPR) via α_1 and α_2 AR activation, as well as increased HR and contractility via β_1 AR activation, thus increasing BP (Gordan et al., 2015).

Vasopressin, also known as antidiuretic hormone, is produced in the hypothalamus, stored in the posterior pituitary gland, and released in response to a reduction in BP, plasma volume, or an increase in plasma osmolarity (Holmes et al., 2004; Gordan et al., 2015). Within the kidney, vasopressin causes water retention by increasing water permeability, which increases blood volume, Q, and thus, BP (Nielson et al., 1995). Vasopressin is also a vasoconstrictor, which increases TPR and BP (Gordan et al., 2015).

The renin-angiotensin-aldosterone system (RAAS) regulates BP and fluid balance (Gordan et al., 2015). Once a decrease in blood volume or BP is detected, renin is released from the kidneys and converts the liver angiotensinogen into angiotensin I (Nguyen et al., 2002). Angiotensin I is further modified by angiotensin converting enzyme (ACE) into angiotensin II, the active form of the hormone. Angiotensin II is a potent vasoconstrictor that directly raises BP by increasing TPR (Nguyen et al., 2002). It also acts on the kidneys to increase sodium reabsorption, which increases water retention and BP (Gordan et al., 2015). Angiotensin II also stimulates aldosterone release from the adrenal cortex, causing sodium retention and leads to an increase in blood volume and BP (Gordan et al., 2015).

Atrial natriuretic peptide (ANP) is a cardiac hormone that increases BP (Gordan

et al., 2015; Potter et al., 2009). Its release is caused by distension of the atria, β-AR stimulation, or increases in angiotensin II, which all lead to an increase in BP (de Bold, 1985).

Endothelin-1 (ET-1) is a potent vasoconstrictor produced by endothelial cells and can counterbalance the activity of local vasodilatory substances (Touyz & Shiffrin, 2003; Gordan et al., 2015). ET-1 is produced in response to chemical (e.g. angiotensin II or catecholamines) or mechanical (e.g. shear stress) stimulation of the endothelium (Touyz & Shiffrin, 2003). Depending on the receptor ET-1 binds to, it can either induce smooth muscle vasoconstriction, resulting in increases in TPR and BP, or cause vasodilation via NO release, thus decreasing TPR and BP (Pollock et al., 1995; Gordan et al., 2015).

Other Factors Regulating Blood Pressure

The concentration of K^+ within skeletal muscle is important to the regulation of BP (Lindinger & Sjogaard, 1991). An increase of $[K^+]$ in the interstitial space causes vasodilation of the vascular bed to help deliver nutrients to the contracting muscle and remove waste products from it, thus reducing TPR and BP (Lindinger & Sjogaard, 1991).

When adenosine triphosphate (ATP) is broken down during smooth muscle contraction, its by-products accumulate, such as adenosine diphosphate, adenosine monophosphate, and adenosine (Haddy & Scott, 1968). During muscle contraction, an increased concentration of adenosine induces vasodilation through its action on the adenosine receptors, thus reducing TPR and BP (Ballard et al., 2014).

1.2.4 Blood Pressure Measurement

The most accurate measure of resting BP involves the insertion of a catheter into the radial artery with a pressure transducer attached to the catheter providing direct

measures of SBP, DBP and MAP (Parati et al., 1989). However, this costly and invasive procedure requires specialized training, which discourages its use in a clinical setting (Parati et al., 1989). Two of the more practical and commonly employed techniques in clinical practice include auscultatory sphygmomanometry and oscillometry (Dieterle, 2012). Both methods are non-invasive and are measured at the level of the brachial artery (Dieterle, 2012). A novel form of oscillometry known as ambulatory BP monitoring has recently gained interest in the clinical community, with evidence suggesting that it is a more reliable measure of BP (Pickering et al, 2005; Sherwood et al., 2012).

Auscultatory Sphygmomanometry

For decades, auscultatory sphygmomanometry was considered the gold standard for BP measurement in clinical practice and clinical research (Campbell et al., 2014; Dieterle, 2012). It is a non-invasive method of BP measurement that utilizes a cuff and sphygmomanometer to detect Korotkoff sounds (Dieterle, 2012; Beevers et al., 2001). However, even with adequate training, it is difficult to ensure accurate measurements with this technique since it requires adequate hearing and concentration to interpret Korotkoff sounds (Campbell et al., 2014). This type of BP measurement can also lead to observer measurement bias, which is when the observer simply adjusts the pressure to meet their expectation (Beevers et al., 2011). Due to these limitations that can lead to the misdiagnosis of HTN, auscultatory sphygmomanometry is not as reliable and accurate as intra-arterial BP measurements (Pickering et al., 2005).

Oscillometry

Similar to auscultatory sphygmomanometry, oscillometry is a non-invasive method that uses cuff inflation to measure BP in AOBP devices (Campbell et al., 2014;

Dieterle, 2012). This technique differs from auscultatory sphygmomanometry in that it employs a microprocessor to detect oscillatory signals (Shahriari et al., 2003). The oscillometric technique has a number of advantages in comparison to auscultatory sphygmomanometry, such as it being less susceptible to external noise disturbance, not relying on human auditory acuity, and not requiring a transducer, which makes the accuracy of cuff placement less critical (Ogedegbe & Pickering, 2010; Pickering et al., 2005). A limiting factor of auscultatory sphygmomanometry is that the algorithms used for detecting SBP and DBP from MAP are different from one device to another, and are not disclosed by the manufacturers (Pickering et al., 2005). However, when compared to auscultatory sphygmomanometry and intra-arterial measurements, the oscillometric technique has shown generally good agreement in terms of BP measurement accuracy (Pickering et al., 2005). This is evident by the fact that the AOBP is now the preferred method of measuring in-office BP (Leung et al., 2016).

Ambulatory Monitoring

Ambulatory BP monitoring uses the oscillometric technique as described above, but can record BP for 24 hours or longer (O'Brien et al., 2001). The same placement of a cuff around the upper arm for assessment of BP at the brachial artery is used, however, the cuff is attached to a monitor by a hose and is programmed to inflate at set time intervals throughout the prescribed measurement period (O'Brien et al., 2001). The ambulatory monitor is generally programmed to measure BP every 30 minutes during the day (6:00 AM – 10:00 PM), and every hour during the night (10:00 PM – 6:00 AM) (Pickering et al., 2006). The BP measures are recorded by the monitor and can be uploaded to a computer to generate mean daytime, nighttime and 24-hour BP

measurements (Pickering et al., 2006; O'Brien et al., 2003).

There has been a growing emphasis on BP readings taken outside of the clinical setting to prevent the white coat effect, which is a phenomenon that leads to increased BP readings at the clinic visit, but normotensive BP readings outside of the clinical setting (Ogedegbe & Pickering, 2010). For example, a study by Graves and colleagues (2003) reported a mean manual BP taken in a clinic to be 152/84 mmHg, while the mean 24-hour ambulatory BP was 138/74 mmHg. Therefore, ambulatory BP monitoring can be used to rule out white-coat HTN and produce a more reliable measure of BP (Drawz et al., 2012). Additionally, BP measurements taken in a health care provider's office are affected by random error, systematic error, as well as several other physiological variables that can affect the patient during the day, whereas BP measurements at night are considered to be basal BP and represent the true BP status of an individual (Mahabala et al., 2013).

Ambulatory BP monitoring can also provide greater insight into the efficacy of antihypertensive medications and the overall changes the medication produces in the BP profile by measuring BP during sleep, an increasingly important prognostic parameter for CVD risk (O'Brien et al., 2001; Boggia et al., 2011). In healthy individuals, BP follows a circadian pattern (Panza et al., 1991). At night, a slight reduction or "dip" of BP is a normal physiological change that can be blunted by CVD risk factors (Mahabala et al., 2013). A patient with a fall >10% in SBP and DBP in the night in comparison to daytime readings is considered normal and is defined as a dipper (Peixoto & White, 2007). Patients with a nocturnal fall <10% are defined as nondippers (Peixoto & White, 2007). In the hypertensive population, a nondipping pattern is correlated with greater rates of

insulin resistance, increased arterial stiffness and increased risk of CVD (Birkenhager & Van den Meiracker, 2007; Anan et al., 2003; Cicek et al., 2013). Therefore, the dipping pattern can be used to investigate the secondary causes of HTN and determine the efficacy of antihypertensive therapies (Mahabala et al., 2013).

1.2.5 Pathophysiology of Hypertension

The progression to HTN results from a combination of environmental, genetic and behavioural factors (DeMarco et al., 2014). Dysfunction in one or more of the BP regulatory pathways can play a role in the development of primary HTN. Several studies have discovered a link between a dysfunctional ANS and HTN development (Singh et al., 2010; Julius & Schork, 1978). A dysfunctional ANS can cause the SNS to be chronically activated, which can contribute to HTN by its effects on the heart, vasculature, and kidneys (Mark, 1996). An over-active SNS is the main reason that most patients with essential HTN have higher levels of circulating plasma catecholamines (E and NE) in comparison to normotensive controls (Goldstein, 1983). This SNS stimulation via NE release from the adrenals results in peripheral vasoconstriction (increased TPR), increased HR, and an elevated resting BP (Singh et al., 2010). A dysfunctional ANS can also decrease parasympathetic activity, which reduces cardiac vagal drive (Mancia & Grassi, 2014). This reduced vagal inhibitory influence on the sinus node can lead to chronic elevations of HR and BP (Julius et al., 1971).

As mentioned previously, the arterial baroreflex has an important role in the regulation of BP. However, chronically high BP results in a stiffer carotid arterial wall, causing the more rigid carotid sinus to be less distensible during a BP increase (Honzikova & Fiser, 2009; Singh et al., 2010). This is supported by the fact that

hypertensive individuals have decreased baroreflex sensitivity in comparison to the normotensive population (Honzikova & Fiser, 2009). Since baroreceptors are a type of mechanoreceptor that are stimulated by distension of the carotid wall, decreased baroreflex sensitivity means less activation of the baroreceptor, leading to a chronically elevated BP set-point (Honzikova & Fiser, 2009). With respect to the RAAS, deviation from normal function can cause the overproduction of circulating renin (Singh et al., 2010). This causes an increased production of angiotensin II and aldosterone, which both contribute to HTN development via increased vasoconstriction and water retention, respectively (Singh et al., 2010; Beevers et al., 2001).

There are many other factors that can contribute to the raised BP seen in the hypertensive population. Insulin resistance is also an underlying mechanism that contributes to the progression of HTN, as well as renal complications in obesity and diabetes (Aroor et al., 2013). Obesity contributes to HTN, since an increased BMI is associated with an increase in plasma volume and Q, which can both increase BP (Carretero & Oparil, 2000; DeMarco et al., 2014). Obesity and a sedentary lifestyle promote insulin resistance, a condition with impaired insulin metabolic signaling response to the liver, skeletal muscle, and adipose tissue (Sowers, 2013; DeMarco et al., 2014). This impairment of signaling decreases the bioavailability of NO, which reduces endothelial-mediated vascular relaxation, causing an increase in TPR and BP (Sowers, 2013). Although obesity is a significant factor associated with insulin resistance, non-obese subjects with HTN are still much more likely to exhibit insulin resistance in comparison to normotensive individuals (Modan et al., 1985). Therefore, it is evident that there are many interrelated factors that contribute to HTN, with the probable role of these

factors differing among individuals (Beevers et al., 2001).

Other lifestyle factors that contribute to essential HTN development include high alcohol intake, high salt intake, low physical activity, low K^+ intake and low Ca^{2+} (Sever & Poulter, 1989; Carretero & Oparil, 2000). Aging is considered a major non-modifiable risk factor in the development of HTN, with studies reporting a significant correlation between aging and increased BP (Harvey et al., 2015; Wang et al., 2010). This increased risk of HTN from aging is due to vascular changes, which causes endothelial dysfunction and increased vascular stiffness (Harvey et al., 2015).

Sex differences can also have an impact on the regulation of BP. Before menopause, women are better protected from most cardiovascular events compared to men (Maranon & Reckelhoff, 2013). After menopause, postmenopausal women are at increased risk of cardiovascular complications compared to premenopausal women and at a similar risk to aged-matched men (Maranon & Reckelhoff, 2013). The sex-based mechanisms for HTN development are not as simple as the presence or absence of androgens, since hormone replacement therapy in both sexes does not appear to provide prevention against cardiovascular events (Maranon & Reckelhoff, 2013).

There are also differences in ethnicity that can contribute to HTN. In a recent meta-analysis of the North American population, it was shown that non-hispanic black individuals have higher rates of HTN in comparison to white individuals, while Indigenous, Chinese, Hispanic and Arab individuals had similar rates of HTN in comparison to white individuals (Gasevic et al., 2015).

1.2.6 Prevention/Treatment of Hypertension

Randomized controlled trials have convincingly shown that treatment of HTN

reduces the risk of stroke by approximately 30%, coronary heart disease by 10-20%, congestive heart failure by 40-50%, and total mortality by 10% (Wang et al., 2005). Meta-regression analyses have also shown relative risk reductions for major CVD events (stroke, heart failure, and all-cause mortality) to be proportional to the magnitude of BP reduction achieved (Ettehad et al., 2016; Lewington et al., 2002). More specifically, reductions as low as 2 mmHg in SBP can reduce the risk of coronary heart disease, stroke, heart failure, and all-cause mortality (Ettehad et al., 2016; Lewington et al., 2002). In addition, reductions in nighttime BP have been associated with increased rates of a normal dipping pattern, significantly lower rates of CVD, and a decreased rate of all-cause mortality (Mehta & Drawz, 2011).

This is supported by recent findings from the SPRINT Research Group who found that treating individuals over 50 years of age with HTN to a SBP target of <120 mmHg in comparison to a target of <140 mmHg resulted in lower rates of fatal and nonfatal major cardiovascular events and death from any cause (SPRINT Research Group, 2015). The results of the SPRINT study add substantial evidence to the benefits of lowering SBP. The SPRINT study has influenced Canadian HTN guidelines, with the treatment goal for most adults with HTN being SBP <140 mmHg and DBP <90 mmHg, while for select high-risk patients, the treatment involves a target of SBP <120 mmHg (Leung et al., 2016).

Engaging in healthy dietary habits and meeting the guidelines for physical activity are essential components in the prevention and management of HTN (Leung et al., 2016). Other lifestyle modifications include stress reduction, smoking cessation and limiting alcohol consumption (Khan et al., 2007). However, it was reported that over

60% of Canadians aged 12 years and older are not meeting the recommended daily intake of fruits and vegetables (Statistics Canada, 2015c). Regular physical activity has also been shown to be an integral element of maintaining a normal BP, but only 15% of adults are meeting the current exercise guidelines of 150 minutes of moderate to vigorous activity per week (WHO, 2017; Statistics Canada, 2014a).

If such modifications are inadequate to generate an acceptable reduction in BP to within target ranges, pharmacological therapy is recommended in addition to lifestyle changes (Brook et al., 2013). Different classes of pharmaceuticals target different pathological mechanisms of HTN; common medications utilized include calcium channel blockers, ACE inhibitors, diuretics, and β-blockers (Chobanian et al., 2003). Calcium channel blockers bind to L-type calcium channels on vascular smooth muscle and cardiac tissue to prevent calcium ion influx into the cell membrane (Livada & Shiloah, 2013). Among other effects, this blockage causes vasodilation of vascular smooth muscle (decrease in TPR) and reduces HR, which both lead to a lower BP (Livada & Shiloah, 2013). ACE inhibitors, which prevent the formation of the vasoconstrictor angiotensin, subsequently decrease TPR and BP (Sweitzer, 2003). Thiazides are the most common type of diuretic used for lowering BP (Duarte & Cooper, 2010). Thiazides decrease sodium reabsorption by inhibiting the sodium/chloride-cotransporter in the renal distal convoluted tubule (Duarte & Cooper, 2010). Acutely, this results in an increased loss of fluids in urine, which leads to decreased extracellular fluid and plasma volume, subsequently reducing Q and BP (Duarte & Cooper, 2010). Chronically, however, thiazides must lower BP through another mechanism since extracellular fluid and plasma volume are typically fully recovered within 6 weeks, yet BP reductions are maintained

(Duarte & Cooper, 2010). Although the mechanism has not been fully elucidated, it has been shown that thiazide diuretics decrease TPR, which maintains the BP reductions in the long term (Duarte & Cooper, 2010). Finally, β-blockers prevent catecholamines from binding to their receptor, causing the heart to pump with less intensity and a reduction in HR and BP (Frishman, 2003). Despite the multitude of pharmacologic treatments available, many Canadians treated pharmacologically for HTN still have BP above target ranges (Statistics Canada, 2014b).

Adherence to lifestyle modifications, such as healthy eating and regular exercise, may also be difficult for certain populations due to physical limitations or lack of functional independence (Schutzer et al., 2004). These findings assert that current HTN interventions do not work for everyone. Novel interventions that can be used independently or as an adjunct to traditional therapies in order to treat HTN must be explored.

1.3 Exercise Training

The Canadian Physical Activity Guidelines recommend at least 150 minutes of moderate to vigorous aerobic exercise per week in healthy adults over the age of 18 years, with dynamic resistance exercise performed at least 2 days per week (Tremblay et al., 2011). These recommendations are supported by guidelines around the world (Thompson et al., 2013; Kahlmeier et al., 2015). For the hypertensive population, the most recent Canadian Physical Activity Guidelines from the Canadian Hypertension Education Program recommend 30-60 minutes of moderate intensity (40 to <60% of an individual's HR reserve) aerobic exercise (e.g. walking, jogging, cycling, or swimming) 4-7 days per week (Leung et al., 2016). The Canadian Hypertension Education Program

also prescribes dynamic resistance training (e.g. free weight lifting, or fixed-weight lifting) as an adjunct to aerobic exercise (Leung et al., 2016). Dynamic resistance training should be performed 2 to 3 times per week while completing 8-12 repetitions per exercise, while focusing on all major muscle groups (Thompson et al., 2013). Until recently, no guidelines or recommendations existed for a specialized form of resistance exercise, isometric resistance training (IRT). IRT involves sustained contractions against an immoveable load or resistance with minimal or no change in length of the muscle involved (Inder et al., 2016). As a result of accumulating evidence, the American Heart Association recently recommended IRT as an alternative method for lowering BP in their 2013 Position Statement (Brook et al., 2013), and handgrip training was suggested as an adjuvant training regimen in the CHEP guidelines (Leung et al., 2016). The most common IRT protocol consists of four, 2-minute sustained contractions performed at 30% of maximal voluntary contraction (MVC) on a handgrip dynamometer, known as isometric handgrip (IHG) training. Session durations range from 12-15 minutes per bout, and are performed at a minimum frequency of 3 times a week over a period of 8-10 weeks (Brook et al., 2013).

IRT also includes isometric leg (IL) exercise, which appears to elicit similar BP-lowering benefits as the IHG. This protocol consists of individuals sitting in an upright position with a 90 degree flexion of the hip, and then multiple, timed leg extensions are performed at a set percentage of MVC (Brook et al., 2013; Baross et al., 2012; Devereux et al., 2010).

1.3.1 Acute Effects of Exercise on Blood Pressure

In general, an acute bout of exercise causes an increase in $PaCO_2$ and $[H^+]$, which

will increase the frequency of impulses relayed to the CCC via afferent feedback (Gordan et al., 2015). This causes an increase in SNS activity and PNS inhibition, resulting in an increase in Q, HR, and vasoconstriction in the venous vasculature, which causes an augmentation in BP in order to restore blood supply to the working tissues (Mayo et al., 1999; MacDonald, 2002; Joyner & Limberg, 2014). There are also receptors within skeletal muscle that help monitor BP and HR during exercise (Murphy et al., 2011). These receptors (mechanoreceptors and metaboreceptors) make neural-mediated cardiovascular adjustments through a peripheral reflex in the contracting muscles known as the exercise pressor reflex (EPR) (see Section 1.2.3) (Murphy et al., 2011).

Aerobic exercise can cause increases in SBP >200 mmHg, while dynamic resistance exercise can cause increases of SBP and DBP up to 400 mmHg and 200 mmHg, respectively (MacDonald, 2002; MacDougall et al., 1985). With respect to acute isometric resistance exercise, Araujo and colleagues (2011) had older, primarily coronary artery disease patients (n = 41; age = 64 ± 9 years; resting BP = 115/69 ± 11/10 mmHg) perform the IHG exercise (four, 2-minute bouts, 1-minute rests, 30% MVC) and reported modest increases in HR (3 ± 4 beats per minute) and BP (16/10 ± 7/6 mmHg). Wiley and colleagues (1992) investigated the effect of a 2-minute IHG contraction at 30% MVC in young normotensive individuals (n = 8; age = 20-35 years; resting BP = 134/87 ± 1/2 mmHg) and found acute mean increases of 17/16 mmHg for SBP/DBP, respectively. In addition, Aoki and colleagues (1983) examined the BP response to an acute bout of IHG (3 minutes, 30% MVC) in normotensive (n = 18; age = 39 ± 3 years; resting BP = 117//73 ± 6/5 mmHg) and non-medicated hypertensive (n = 50; age = 41 ± 4 years; resting BP = 162/105 ± 13/9 mmHg) men. It was reported that the hypertensive men had

a larger mean increase in BP during the IHG bout (45/30 mmHg) in comparison to the normotensive men (30/26 mmHg). Since the hypertensive population already has a higher initial BP and has been shown to display greater increases in BP during an IHG bout, caution should be used when working with this population.

Recent work by Carlson and colleagues (2017) measured BP, HR, and rate pressure product, a measure of myocardial oxygen consumption in normotensive (n = 60; age = 39 ± 9 years; resting BP = 115/67 ± 11/7 mmHg) and pre-hypertensive (n = 60; age = 54 ± 7 years; resting BP = 131/75 ± 13/8 mmHg) individuals performing IHG (four, 2-minute bouts conducted unilaterally in the non-dominant hand with 3-minute breaks between sets) at either 5%, 10%, or 30% of their MVC. No significant difference between groups were found for peak SBP, DBP, MAP, HR, or rate pressure product across any of the four bouts of IHG in any of the three groups (5%, 10%, or 30% MVC) (Carlson et al., 2017). Additionally, the low-to-moderate intensity of the IHG exercise has been shown to be safe, with no reports of lasting physical impairments or significant unfavourable clinical events in over 25,000 sessions recorded (Millar et al., 2014).

Acute exercise can cause SBP and DBP 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, while up to 10 hours following bouts of dynamic resistance exercise in hypertensive individuals (Rondon et al., 2002; Melo et al., 2006). Generally, it has been found that PEH occurs independently of exercise intensity when directly comparing exercise intensities, but it seems that a minimum intensity (e.g. 30% of maximal exercise capacity) is needed to produce PEH (MacDonald, 2002).

Although there is evidence to support that that a longer duration of exercise produces a greater magnitude of PEH (45 minutes of aerobic exercise compared to 25 minutes) (Forjaz et al., 1998), the findings are preliminary and warrant further investigation (MacDonald, 2002). Average reductions in SBP/DBP of 8/9 mmHg and 10/7 mmHg immediately following a bout of aerobic exercise (PEH) have been reported in normotensive and hypertensive populations, respectively (MacDonald, 2002). Reductions in post-exercise BP in response to dynamic resistance exercise for SBP are similar to those of aerobic exercise, however changes in DBP remain inconclusive (Anunciacao & Polito, 2011). In aerobic exercise, the magnitude of BP reduction is proportional to pre-exercise resting BP in both BP populations; individuals with the highest pre-exercise values experience the greatest reductions post-exercise, while those with the lowest pre-exercise values experience the slightest reductions (Rondon et al., 2002). This effect has not been observed following dynamic resistance exercise (MacDonald, 2002). The mechanisms underlying PEH are elusive, but a sustained inhibition of sympathetic outflow and release of local vasodilatory substances have been implicated (MacDonald, 2002).

The effect of acute IRT exercise on PEH is under-investigated. A study conducted by Millar and colleagues (2009) observed PEH of SBP (3 mmHg) following four, 2-minute sustained bilateral IHG contractions at 30% MVC in older normotensive individuals (n = 18; age = 70 ± 5 years; resting BP = 125/69 ± 4/1 mmHg). Additionally, O'Driscoll and colleagues (2017) examined the effects of isometric wall squats (four, 2-minute holds with 2-minutes of rest in between each set) on non-medicated, pre-hypertensive men (n = 26; age = 45 ± 8 years; resting BP = 133/78 ± 6/9 mmHg) and

found significant mean post-exercise reductions in SBP and DBP of 23 and 19 mmHg, respectively. Investigators noted that this bout of IRT lead to a significant improvement in cardiac function and mechanics acutely, which may be partly responsible for the observed BP reductions in IRT when used chronically (O'Driscoll et al., 2017). In contrast, PEH was not observed by Bartol and colleagues (2012) in well-controlled medicated hypertensives (n = 11; age = 60 ± 9 years; resting BP = 114/61 ± 13/12 mmHg) within 22 hours following four, 2 minute sustained bilateral contractions at 30% MVC. These findings were replicated by Olher and colleagues (2013) in well-controlled medicated hypertensive elderly women (n = 12; age = 64 ± 1 years; resting BP = 121/72 ± 7/6 mmHg) following a bout of either four, 2 minute sustained bilateral contractions at 30% MVC or four, 45 second sustained unilateral contractions at 50% MVC. The lack of a PEH response observed in this population may be attributed to the BP modulating effects of antihypertensive medication.

1.3.2 Chronic Effects of Exercise on Blood Pressure

The effectiveness of chronic exercise-induced reductions in resting BP has been well proven. Aerobic exercise interventions lasting ≥4 weeks have been shown to produce an average resting SBP/DBP reduction of approximately 2/2 mmHg and 6/5 mmHg in normotensives and hypertensives, respectively, despite the utilization of various of exercise modalities (walking, running, cycling), intensities (45-86% of maximal oxygen reserve), durations (15-60 minutes) and frequencies (1-5 days per week) (Kelley et al., 2001). The weight of the evidence suggests that chronic dynamic resistance exercise reduces resting BP, although the amount of supporting evidence is not nearly as extensive as that with aerobic training (Cardoso et al., 2010). A meta-analysis of 25

randomized controlled trials of dynamic resistance training lasting ≥6 weeks, ≥2 times per week, and ≥30% of 1 repetition maximum, as well as 3 randomized controlled trials of IRT lasting ≥8 weeks, ≥2 times per week, and ≥30% MVC reported a significant SBP/DBP reduction (4/4 mmHg) in normotensive groups, while in hypertensive groups, the reduction of (4/2 mmHg) was not significant (Cornelissen et al., 2011). It should be noted that only 6 studies (4 dynamic resistance exercise and 2 IRT) in the meta-analysis examined the effects of resistance exercise on BP in the hypertensive population (Cornelissen et al., 2011). However, recent studies on dynamic resistance exercise training in the hypertensive population have shown a more consistent resting BP-lowering effect. A study conducted by da Cunha Nascimento and colleagues (2014) in older, hypertensive women (n = 12; age = 67 ± 6 years; resting BP = 130/81 ± 8/8 mmHg) reported mean reductions in SBP/DBP by an average of 18/10 mmHg after 12 weeks of dynamic resistance exercise. Likewise, a study conducted by Moraes and colleagues (2012) in hypertensive, middle-aged men (n = 15, age = 46 ± 3 years, resting BP = 150/93 ± 3/2 mmHg) reported significantly reduced SBP/DBP by an average of 16/12 mmHg following 12 weeks of dynamic resistance exercise. It important to note that this study had more repetitions and less rest between sets in comparison to other dynamic resistance exercise training protocols in the past, which could account for the increased magnitude of BP reductions (Moraes et al., 2012).

Numerous studies provide compelling evidence that IRT results in reductions of resting BP in a variety of populations (Millar et al., 2014; Carlson et al., 2014; Lawrence et al., 2015). A meta-analysis of 11 randomized control trials (6 IHG and 5 IL studies) lasting >3 weeks, ≥3 times per week, at varying intensities (8%-40% MVC, 75%-95% of

maximum HR achieved during an MVC) assessed the IRT effect on resting BP in normotensive and hypertensive individuals (n = 302; age ≥18 years) (Inder et al., 2016). The mean reductions observed after IRT were 5 mmHg in SBP and 4 mmHg in DBP (Inder et al., 2016).

In general, IRT for ≥8 weeks demonstrate a larger reduction in SBP (7 vs. 3 mmHg) and MAP (4 vs. 2 mmHg) in comparison to those who trained for <8 weeks, with no difference for change in DBP between the duration categories (Inder et al., 2016). It has also been reported by Millar and colleagues (2014) that there is a strong correlation between the magnitude of change following IRT and baseline BP, such that the greatest reductions are observed in those with higher pre-training BP. No IHG trials lasting longer than 10 weeks have been reported, which makes the BP response to IHG beyond 10 weeks unknown (Lawrence et al., 2015). In addition, there is little information on the volume of IHG training needed to maintain BP adaptions after a significant reduction in BP is achieved (Lawrence et al., 2015). In the only known study investigating the effects of IHG training frequency, Badrov and colleagues (2013a) examined the effects of IHG training 3 (IHG3) or 5 (IHG5) times per week (four, 2-minute unilateral IHG contractions at 30% MVC for 8 weeks) on BP reductions in normotensive women (IHG3 group: n = 12; age = 23 ± 4 years; resting BP = 94/57 ± 6/7 mmHg; IHG5 group: n = 11; age = 27 ± 6 years; resting BP = 97/57 ± 11/7 mmHg). Although both groups produced equivalent reductions of 6 mmHg in SBP at the conclusion of the 8-week intervention, only the IHG5 group experienced significant BP-lowering after 4 weeks of training. However, nothing is known about how much IRT is required in other populations to retain BP adaptions once a significant BP reduction is achieved (Lawrence et al., 2015).

Despite the apparent effectiveness of IHG training on resting BP, there is data to suggest that there is inter-individual variability in training responsiveness. Millar and colleagues (2008) found that post-menopausal women experienced greater training-induced reductions in resting BP in comparison to age-matched men. In contrast, Somani (2015), as well as Badrov and colleagues (2016) provided evidence that IHG training is equally effective in reducing resting BP in young normotensive men and women. In addition, the recent meta-analysis by Inder and colleagues (2016) found that men reduce MAP more than women (4 mmHg vs. 2 mmHg), while there were no significant differences for change in SBP, DBP, or HR between men and women. Inder et al. (2016) also noted that individuals ≥45 years of age experience larger reductions in MAP than those <45 years of age with IHG training (6 mmHg vs. 3 mmHg) (Inder et al., 2016).

Although not as commonly studied, IL exercise appears to elicit similar BP-lowering benefits in normotensives despite it being less investigated in comparison to IHG. Previous studies have used a wide range of IL training intensities, either based on the participant's MVC force (20-50%), using a specific percentage of maximum HR achieved during an MVC, or by measuring muscle activation using electromyography (EMG) (10-30% of peak EMG) (Gill et al., 2015; Inder et al., 2016). The typical training protocol consists of four, 2-minute bouts of double-leg isometric exercise separated by 3-minute rest periods, 3 times per week for 4 to 8 weeks (Gill et al., 2015).

Inder and colleagues (2016) reported, in their meta-analysis, that participants undertaking IL training demonstrated a smaller reduction in SBP in comparison to IHG training (4 vs. 7 mmHg) (Inder et al., 2016). Devereux and colleagues (2010) observed mean reductions in both SBP/DBP of 5/3 mmHg in a normotensive population (n = 13;

age = 21 ± 2 years; resting BP = 120/69 ± 12/4 mmHg) following 4 weeks of bilateral leg training conducted 3 times per week. The training protocol involved four, 2 minute sustained leg extensions at 24% of MVC. Similarly, Baross and colleagues (2012) investigated the effects of high intensity (14% MVC) IL training in comparison to low intensity (8% MVC) IL training in healthy middle-aged men (14% MVC group: n = 10; age = 55 ± 5 years; resting BP = 139/78 ± 7/6 mmHg; 8% MVC group: n = 10; age = 54 ± 5 years; resting BP = 137/78 ± 5/5 mmHg), performed 3 times per week for 8 weeks (four, 2 minute bilateral leg contractions). Those who trained at high intensity (14% MVC) experienced mean SBP and MAP reductions of 11 and 5 mmHg, respectively, with no change in DBP. Conversely, the low intensity group (8% MVC) did not experience significant reductions in BP (Baross et al., 2012). IL training has yet to be investigated in the hypertensive population, requiring additional research to determine its efficacy as a method of HTN control/management.

A growing body of evidence suggests that IHG training is particularly beneficial to individuals with HTN. This work has contributed to the endorsement of IHG training as an alternative form of HTN management (Brook et al., 2013; Leung et al., 2016), as previously noted (see Section 1.3). It has been reported that hypertensive participants experience greater mean reductions of MAP in comparison to normotensive participants (6 vs. 3 mmHg), while there were no significant differences for change in SBP or DBP between populations (Inder et al., 2016). Taylor and colleagues (2003) examined the effects of IHG training on resting BP in older adults with uncontrolled HTN (n = 9; age = 69 ± 6 years; resting BP = 156/82 ± 9/9 mmHg) with 75% of participants taking antihypertensive medication at the time. IHG was performed 3 times per week for 10

weeks, with training consisting of four, 2-minute bilateral contractions at 30% MVC. IHG training resulted in a significant reduction in SBP (156 ± 9 mmHg to 137 ± 8 mmHg) and MAP (107 ± 9 mmHg to 96 ± 9 mmHg). Although there was a downward trend in DBP, the difference was not statistically significant. Investigators did not separate the medicated and non-medicated participants, and as a result, there is no way of differentiating the exact response of medicated and non-medicated BP adaptations to IHG in this population.

Three studies have examined the effects of IHG on medicated hypertensives with borderline to uncontrolled HTN (McGowan et al., 2006b; Millar et al., 2013; Badrov et al., 2013b). In the study by Millar et al. (2013), participants (n = 13; age = 65 ± 6 years; resting BP = 125/78 ± 12/2 mmHg) conducted four, 2-minute unilateral bouts at 30% MVC, 3 times per week for 8 weeks. IHG training resulted in a significant reduction in SBP (125 ± 3 mmHg to 120 ± 2 mmHg) and MAP (90 ± 2 mmHg to 87 ± 2 mmHg). Similarly, Badrov et al. (2013b) trained participants (n = 12; age = 65 ± 7 years; resting BP = 129/72 ± 16/9 mmHg) 3 times per week for 10 weeks (four, 2-minute bilateral bouts at 30% MVC). IHG training resulted in significant reductions of SBP (129 ± 16 mmHg to 121 ± 16 mmHg), MAP (91 ± 11 mmHg to 85 ± 10 mmHg), and DBP (72 ± 9 mmHg to 67 ± 8 mmHg). In a similar aged cohort, McGowan et al. (2006b) examined the effects of 8-weeks of bilateral (n = 7; age = 62 ± 4 years; resting BP = 134/73 ± 5/3 mmHg; four, 2-minute bilateral bouts at 30% MVC with 1-minute rest periods) or unilateral (n = 9; age = 66 ± 6 years; resting BP = 142/80 ± 4/4 mmHg; four, 2-minute unilateral bouts at 30% MVC with 4-minute rest periods) IHG training on resting BP. Investigators reported post-training SBP reductions compared to baseline with bilateral

training (134 ± 5 mmHg to 118 ± 4 mmHg) and unilateral training (142 ± 4 mmHg to 132 ± 4 mmHg). DBP remained unchanged from baseline after both interventions, while MAP was not reported.

The effect of exercise on ambulatory BP is under-investigated. Recent meta-analyses of randomized controlled trials suggest that aerobic exercise can produce mean reductions in daytime ambulatory SBP/DBP for normotensives and hypertensives of approximately 3/3 mmHg and 7/5 mmHg, respectively, but it does not affect nighttime BP in either population (Cornelissen et al., 2013; Fagard, 2006). Only two studies to date have examined ambulatory BP following a dynamic resistance exercise protocol (Blumenthal et al., 1991; Van Hoof et al., 1996). No changes in ambulatory BP measures were shown in either a hypertensive or normotensive population, but the lack of data addressing the issue makes any conclusion premature.

There have only been two studies examining the effects of IRT on ambulatory BP (Somani et al., 2017; Stiller-Moldovan et al., 2012). Somani and colleagues (2017) reported that 10 weeks of IHG training (four, 2-minute bilateral contractions at 30% MVC) in young normotensive men (n = 13; age = 24 ± 4 years; resting BP = 117/65 ± 5/7 mmHg) and women (n = 11; age = 25 ± 5 years; resting BP = 103/62 ± 5/8 mmHg) led to significant reductions in mean 24-hour (men: 4 mmHg; women: 4 mmHg), daytime (men: 3 mmHg; women: 4 mmHg), and nighttime (men: 4 mmHg; women: 3 mmHg) ambulatory SBP measures. Additionally, these reductions in ambulatory BP were associated with reductions in resting SBP in both men and women (Somani et al., 2017). In contrast, Stiller-Moldovan and colleagues (2012) trained well-controlled medicated hypertensive participants (n = 11; age = 60 ± 9 years; resting BP = 114/61 ± 13/12

mmHg) using the traditional bilateral IHG protocol for 8 weeks. IHG training did not significantly change ambulatory BP, but there were clinically relevant reductions in mean 24-hour (3 mmHg) and nighttime SBP (4 mmHg). As mentioned in Section 1.2.6, reductions as slight as 2 mmHg in SBP have been shown to significantly reduce stroke and ischemic heart disease related mortality (Lewington et al., 2002). Additionally, IHG training did not significantly change resting SBP and DBP in either group (Stiller-Moldovan et al., 2012). The BP lowering effects of the antihypertensive medication may have hindered the BP reduction response in this sample. Since there were no significant reductions in resting BP found in the study, it is not known whether reductions in resting BP from IRT are associated with reductions in ambulatory BP as well. A longer training duration or a higher frequency of training may have elicited significant reductions in BP in this population, however this is speculative as their BP is already well controlled on antihypertensive medication. Further investigation is warranted to determine whether IHG training attenuates ambulatory BP in normotensive and well-controlled hypertensive populations.

The mechanisms responsible for many of the observed aerobic and resistance training-induced reductions in BP remain equivocal (Pescatello et al., 2005; Queiroz et al., 2010; Millar et al., 2014). A reduction in SNS activity from aerobic exercise training may hinder NE release, reducing vascular resistance and BP (Pescatello et al., 2005). BP reductions from aerobic exercise are also thought to occur through local mechanisms, such as increased NO release and a reduction in circulating ET-1 constriction factor, resulting in decreased TPR and BP (Pescatello et al., 2004). Chronic dynamic resistance exercise does not seem to modify TPR or SNS activity, which makes the mechanisms for

the BP reductions unclear at this time (Queiroz et al., 2010).

Prominent hypothesized mechanisms of IRT-induced BP reduction include improved modulation of the ANS and well as enhanced vascular function. Heart rate variability (HRV) is a simple and effective non-invasive method used to measure ANS activity (Sztajzel, 2004). Taylor and colleagues (2003) reported significant improvements in HRV in hypertensives concomitant to the BP reductions previously reported (see Section 1.3.2), which suggests improved autonomic balance following the 10 weeks of IHG training. In contrast, Badrov et al., (2013a) found no changes in HRV following BP-lowering IHG training in a similar cohort. Consequently, the role of the ANS in IRT-induced reductions in BP remains unclear.

Flow-mediated dilation (FMD) is an indirect measure of endothelial function and correlates with post-exercise reductions in TPR (Harvey et al., 2005). McGowan and colleagues (2006b) investigated the effects of IHG training on FMD in medicated hypertensives following 8 weeks of bilateral (n = 7; age = 62 ± 4 years; resting BP = 134/73 ± 5/3 mmHg) or unilateral (n = 9; age = 66 ± 6 years; resting BP = 142/80 ± 4/4 mmHg) IHG training conducted 3 times per week. The investigators observed that endothelium dependent vasodilation improved locally only within the trained limbs of participants, concluding that improvements in endothelial function were not systemic and likely did not play a role in the IHG training-induced BP reductions in this cohort.

In contrast, Badrov and colleagues (2013a) reported that 8 weeks of IHG training in young normotensive women conducted 3 times per week (IHG3 group: n = 12; age = 23 ± 4 years; resting BP = 94/57 ± 6/7 mmHg) and 5 times per week (IHG5 group: n = 11; age = 27 ± 6 years; resting BP = 97/57 ± 11/7 mmHg) revealed reductions in SBP and

improvements in resistance vessel endothelial function. However, McGowan et al. (2007) found no changes in FMD in young normotensives (n = 13; age = 28 ± 14 years; resting BP = 119/65 ± 7/7 mmHg) following 8 weeks of IHG training, however FMD reflects peak dilatory response and not basal-level changes in vascular function. Differences of these studies may provide insight into the BP-reducing mechanism of IRT. Comparing the older medicated hypertensive group (McGowan et al., 2006b) to the younger normotensive group (McGowan et al., 2007), it is possible that in the former group, the pharmacological effect on NO release from the medication was enhanced by the isometric stress, resulting in an improved FMD (Lawrence et al., 2015).

1.4 Cardiovascular Reactivity

Of great and recent interest, there is accumulating evidence to suggest that in normotensive individuals of all ages, cardiovascular reactivity to simple cardiovascular stressors (e.g., a simple math task known as the serial subtraction task (SST), or a 2-minute IHG task) can predict the responsiveness to IRT (Millar et al., 2009; Somani 2015). Cardiovascular reactivity refers to the magnitude of change observed in BP and HR measurements during exposure to the stressor from baseline or resting measures (Gerin et al., 2000). It is hypothesized that acute BP elevations in response to a stressor with repeated exposure can produce chronic elevations in resting BP over time and subsequently lead to the development of HTN (Gerin et al., 2000).

Somani (2015) investigated the relationship between cardiovascular reactivity and IHG-training induced reductions in resting BP in a young normotensive cohort of men (n = 13; age = 24 ± 4 years; resting BP = 117/65 ± 5/7 mmHg) and women (n = 13; age = 25 ± 5 years; resting BP = 103/62 ± 5/8 mmHg). Reductions in resting SBP in both men and

women were significantly correlated with SBP reactivity to a 2-minute IHG task. Therefore, individuals with higher SBP reactivity (greater increase in SBP during the IHG task compared to baseline value) were shown to have the greatest reductions in SBP over the 10 weeks of training, while those with lower SBP reactivity produced modest reductions in SBP over 10 weeks. However, the reductions in SBP measures were not correlated with the SST (Somani, 2015). In contrast, Millar and colleagues (2009) reported that cardiovascular reactivity to the SST was significantly correlated with IHG training-induced changes in resting BP in older normotensive participants (n = 17; age = 62 ± 2 years; resting BP = 125/69 ± 4/1 mmHg) following 8 weeks of IHG training. A possible reason for the discrepancy is that younger participants may have a different cardiovascular response to SST in comparison to the older participants.

Badrov et al. (2013b) investigated whether cardiovascular reactivity to the SST and the IHG task was associated with IHG training-induced changes in resting BP in hypertensive individuals (n = 12; age = 65 ± 7 years; resting BP = 129/72 ± 16/9 mmHg). The investigators demonstrated that both stressors were predictive of IHG training responsiveness. Furthermore, like the SST, the IHG may be a promising tool to identify individuals in this cohort that will respond favourably to IHG training.

SBP reactivity to either the SST or the IHG task, however, is not predictive of reductions in 24-hour ambulatory SBP in the young, normotensive population (Somani et al., 2017). However, this work is preliminary, and predicting reductions in ambulatory BP via cardiovascular stressors has yet to be explored in the hypertensive population.

1.5 Detraining Effects on Blood Pressure

Aerobic, dynamic resistance, and IRT have all been shown to significantly reduce

BP (Brook et al., 2013). However, the effect on BP once chronic exercise training has stopped, known as training cessation or detraining, is much less conclusive. The BP lowering effects of aerobic exercise training has been shown to diminish within the early weeks following training cessation, causing BP to return to baseline values (Meredith et al., 1990; Murray et al., 2006). For example, a study by Murray and colleagues (2006) assessed the effect of 4 weeks of aerobic exercise (cycle ergometry; 30 minutes at 60% maximum oxygen consumption, 3-4 times per week) on young normotensive men (n = 17; age = 22 ± 2 years; resting BP = 121/66 ± 7/6 mmHg). The 4-week exercise protocol resulted in significant reductions in SBP (121 ± 7 mmHg to 107 ± 6 mmHg) and DBP (66 ± 6 mmHg to 53 ± 7 mmHg), but BP readings returned to pretraining levels within 2 weeks following training cessation (Murray et al., 2006). The same pattern has been observed in rats, with a significant decrease in BP during the aerobic training protocol, and a time-dependent increase of BP to baseline values during the detraining period (Kilic-Erkek et al., 2016). Only two studies have examined the detraining effect of aerobic exercise on ambulatory BP. In the studies by Somers et al. (1991) and Zanettini et al. (1997), aerobic exercise conducted for 6 months and 4 months in hypertensive participants resulted in a significant reduction in resting SBP and DBP, as well as 24-hour SBP and DBP, but these values returned to baseline 4 months and 2 months after training cessation, respectively. The results emphasize the importance of continued aerobic exercise as part of a healthy lifestyle in the HTN population or in individuals at risk for HTN.

Recent studies on dynamic resistance exercise training in the hypertensive population have shown a significant impact on BP reduction. As reported in Section

1.3.2, the study conducted by Moraes and colleagues (2012) in hypertensive, middle-aged men reported significantly reduced SBP/DBP following 12 weeks of dynamic resistance exercise. BP values remained low during a 4-week detraining period. This was the first resistance exercise study to examine the effects of detraining on BP in hypertensive individuals. Likewise, a study conducted by da Cunha Nascimento and colleagues (2014) in older hypertensive women (see Section 1.3.2) demonstrated training-induced reductions in resting BP after a 12-week dynamic resistance program were also sustained after 4 weeks of detraining.

Four studies have reported on the effects of detraining following IRT. As reported in Section 1.3.2, Wiley and colleagues (1992) found significant reductions in resting SBP following 5 weeks of IHG training in young normotensive participants. These reductions were reversed after only 2 weeks of detraining and gradually returned to pre-training values after 5 weeks (the time course of the training period) (Wiley et al., 1992). More recently, a study by Howden and colleagues (2002) conducted IL training (four, 2-minute bilateral bouts at 20% MVC) in young normotensive participants (n = 8, age = 21 ± 1 years; resting BP = 121/70 ± 10/7 mmHg) 3 times per week for 5 weeks. The significant mean reduction in resting SBP (10 mmHg) was lost after 10 days of detraining (Howden et al., 2002). In a study by Devereux and colleagues (2010), the detraining effect was also observed from IL training (four, 2-minute bilateral bouts at 24% MVC, 3 times per week for 4 weeks) in young, normotensive participants (n = 13; age = 21 ± 2 years; resting BP = 120/69 ± 12/4 mmHg). Significant mean reductions in resting SBP (5 mmHg) were lost after 7 days of training cessation (Devereux et al., 2010). Conversely, a sub-study by McGowan (2006a) in medicated hypertensive

participants (n = 9; age = 66 ± 6 years; resting BP = 142/80 ± 4/4 mmHg) reported that training-induced SBP reductions were maintained in 5 participants followed over a detraining period. These reductions were maintained following both 4 weeks and 8 weeks of training cessation. Although the results should be interpreted with caution due to the small sample size, these preliminary findings suggest HTN status and/or anti-hypertensive medication may play a role in the discrepant findings.

1.6 Summary

In summary, HTN is a major prognostic indicator of CVD, affecting over 26.4% of adults worldwide, and responsible for almost 14% of deaths globally (WHO, 2017; Kearney et al., 2005; Lawes et al., 2008). Randomized controlled trials have convincingly shown that a reduction of 5 mmHg in SBP can reduce the risk of coronary heart disease by 8%, stroke by 13%, heart failure by 14%, and all-cause mortality by 6% (Ettehad et al., 2016). Meta-regression analyses have also shown relative risk reductions for major CVD events (stroke, heart failure, and all-cause mortality) to be proportional to the magnitude of BP reduction achieved (Ettehad et al., 2016; Lewington et al., 2002). These findings are critical because clinically meaningful reductions as slight as 2 mmHg in SBP have been shown to significantly reduce stroke and ischemic heart disease related mortality (Lewington et al., 2002). In addition, reductions in nighttime BP have been associated with increased rates of a normal dipping pattern, significantly lower rates of CVD, and a decreased rate of all-cause mortality (Mehta & Drawz, 2011). For a myriad of reasons, current pharmacological and/or lifestyle interventions for HTN management are not effective for everyone, and numerous individuals with HTN in North America are living with uncontrolled HTN (Wang & Vasan, 2005; Campbell et al., 2013). This is

concerning, as uncontrolled BP substantially increases the risk for HTN-related, often fatal complications. This creates the need for novel and effective BP-lowering treatment tools such as IHG training, which has proven effective in both normotensive and hypertensive populations (Inder et al., 2016; Carlson et al., 2014; Millar et al., 2014), that can be used alone or in conjunction with traditional strategies.

Individuals with higher resting BP appear to experience the greatest reductions in post-BP (Badrov et al., 2013a; Millar et al., 2007), highlighting the potential therapeutic benefit for those with BP above clinical target ranges. Gaining insight into how much training is needed to sustain the BP-lowering effects of IRT has significant clinical applicability, yet remains inconclusive. Furthermore, the cardiovascular reactivity response to an IHG task may be a promising tool to identify individuals that will respond favourably to IHG training.

In conclusion, IHG training has been shown to reduce both resting and ambulatory BP in hypertensive individuals with 8 weeks of training, yet the effects of detraining on BP in this population warrants further investigation. In addition, cardiovascular reactivity to an IHG task to predict the effectiveness of IHG training in reducing ambulatory BP in this patient cohort has yet to be explored.

1.7 References

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

Allen, M., Kelly, K., & Fleming, I. (2013). Hypertension in elderly patients recommended systolic targets are not evidence based. *Canadian Family Physician*, *59*, 19-21.

American Heart Association (2016). Understanding blood pressure readings. Retrieved from: http://www.heart.org/HEARTORG/Conditions/HighBloodPressure/KnowYourNumbers/Understanding-Blood-Pressure-Readings_UCM_301764_Article.jsp#.WUl1vBPyuRs

Anan, F., Takahashi, N., Ooie, T., Yufu, K., Saikawa, T., & Yoshimatsu, H. (2003). Role of insulin resistance in nondipper essential hypertensive patients. *Hypertension Research*, *26*, 669-676.

Anunciacao, P. G., & Polito, M. D. (2011). A review on post-exercise hypotension in hypertensive individuals. *Arquivos Brasileiros de Cardiologia*, *96*, 425-426.

Aoki, K., Sato, K., Kondo, S., Pyon, C. B., & Yamamoto, M. (1983). Increased response of blood pressure to rest and handgrip in subjects with essential hypertension. *Japanese Circulation Journal*, *47*, 802-809.

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

Aroor, A. R., McKarns, S., DeMarco, V. G., Jia, G., & Sowers, J. R. (2013). Maladaptive immune and inflammatory pathways lead to cardiovascular insulin resistance. *Metabolism*, *62*, 1543-1552.

Badrov, M. B., Bartol, C. L., DiBartolomeo, M. A., Millar, P. J., McNevin, N. H., & McGowan, C. L. (2013a). Effects of isometric handgrip training dose on resting blood pressure and resistance vessel endothelial function in normotensive women. *European Journal of Applied Physiology*, *113*, 2091-2100.

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

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

Ballard, H. J. (2014). ATP and adenosine in the regulation of skeletal muscle blood flow during exercise. *Acta Physiologica Sinica*, *66*, 67-78.

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, 2012,* 96497.

Bartol, C., Kenno, K. A., & McGowan, C. L. (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.

Belli, J. F. C., Bacal, F., Bocchi, E. A., & Guimarães, G. V. (2011). Ergoreflex activity in heart failure. *Arquivos Brasileiros de Cardiologia*, *97*, 171-178.

Birkenhager, A. M., & Van den Meiracker, A. H. (2007). Causes and consequences of a non-dipping blood pressure profile. *Netherlands Journal of Medicine*, *65*, 127-31.

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.

Boggia, J., Thijs, L., Hansen, T. W., Li, Y., Kikuya, M., Björklund-Bodegård, K., ... & Dolan, E. (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. *Pharmacological Reviews*, *51*, 651-690.

Brook, R. D., Appel, L. J., Rubenfire, M., Ogedegbe, G., Bisognano, J. D., Elliott, W. J., ... & Townsend, R. R. (2013). Beyond medications and diet: alternative approaches to lowering blood pressure. *Hypertension*, *61*, 1360-1383.

Calhoun, D. A., Jones, D., Textor, S., Goff, D. C., Murphy, T. P., Toto, R. D., ... & Ferdinand, K. (2008). Resistant hypertension: diagnosis, evaluation, and treatment. *Circulation*, *117*, e510-e526.

Campbell, N. R., McAlister, F. A., Quan, H., & Force, H. O. R. T. (2013). Monitoring and evaluating efforts to control hypertension in Canada: why, how, and what it tells us needs to be done about current care gaps. *Canadian Journal of Cardiology*, *29*, 564-570.

Campbell, N. R., Berbari, A. E., Cloutier, L., Gelfer, M., Kenerson, J. G., Khalsa, T. K., ... & Myers, M. G. (2014). Policy statement of the world hypertension league on noninvasive blood pressure measurement devices and blood pressure measurement in the clinical or community setting. *The Journal of Clinical Hypertension*, *16*, 320-322.

Cardoso Jr, C. G., Gomides, R. S., Queiroz, A. C. C., Pinto, L. G., Lobo, F. D. S., Tinucci, T., ... & Forjaz, C. L. D. M. (2010). Acute and chronic effects of aerobic and resistance exercise on ambulatory blood pressure. *Clinics*, *65*, 317-325.

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

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

Carretero, O. A., & Oparil, S. (2000). Essential hypertension. *Circulation*, *101*, 329-335.

Charkoudian, N., Joyner, M. J., Johnson, C. P., Eisenach, J. H., Dietz, N. M., & Wallin, B. G. (2005). Balance between cardiac output and sympathetic nerve activity in resting humans: role in arterial pressure regulation. *The Journal of Physiology, 568,* 315-321.

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. V., Bakris, G. L., Black, H. R., Cushman, W. C., Green, L. A., Izzo Jr, J. L., ... & Roccella, E. J. (2003). The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *Journal of the American Medical Association*, *289*, 2560-2571.

Cicek, Y., Durakoglugil, M. E., Kocaman, S. A., Cetin, M., Erdogan, T., Dogan, S., ... & Canga, A. (2013). Non-dipping pattern in untreated hypertensive patients is related to increased pulse wave velocity independent of raised nocturnal blood pressure. *Blood Pressure*, *22*, 34-38.

Conference Board of Canada. (2010). The Canadian Heart Health Strategy: Risk Factors and Future Cost Implications. Retrieved from: http://www.conferenceboard.ca/e-library/abstract.aspx?did=3447

Cornelissen, V. A., Fagard, R. H., Coeckelberghs, E., & Vanhees, L. (2011). Impact of resistance training on blood pressure and other cardiovascular risk factors a meta-analysis of randomized, controlled trials. *Hypertension*, *58*, 950-958.

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*, 1-9.

da Cunha Nascimento, D., Tibana, R. A., Benik, F. M., Fontana, K. E., Neto, F. R., de Santana, F. S., ... & Balsamo, S. (2014). Sustained effect of resistance training on blood pressure and hand grip strength following a detraining period in elderly hypertensive women: a pilot study. *Clinical Interventions in Aging*, *9*, 219-225.

De Bold, A. J. (1985). Atrial natriuretic factor: a hormone produced by the heart. *Science*, *230*, 767-770.

DeMarco, V. G., Aroor, A. R., & Sowers, J. R. (2014). The pathophysiology of hypertension in patients with obesity. *Nature Reviews Endocrinology*, *10*, 364-376.

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.

Dieterle, T. (2012). Blood pressure measurement–an overview. *Swiss Medicine Weekly*, *142*, w13517.

Duarte, J. D., & Cooper-DeHoff, R. M. (2010). Mechanisms for blood pressure lowering and metabolic effects of thiazide and thiazide-like diuretics. *Expert Review of Cardiovascular Therapy*, *8*, 793-802.

Ettehad, D., Emdin, C. A., Kiran, A., Anderson, S. G., Callender, T., Emberson, J., ... & Rahimi, K. (2016). Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *The Lancet*, *387*, 957-967.

Fagard, R. H. (2006). Exercise is good for your blood pressure: effects of endurance training and resistance training. *Clinical and Experimental Pharmacology and Physiology*, *33*, 853-856.

Forjaz, C. L. D. M., Santaella, D. F., Rezende, L. O., Barretto, A. C. P., & Negrão, C. E. (1998). Exercise duration determines the magnitude and duration of post-exercise hypotension. *Arquivos Brasileiros de Cardiologia*, *70*, 99-104.

Frishman, W. H. (1988). Beta-adrenergic blockers. *The Medical Clinics of North America*, *72*, 37-81.

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

Gasevic, D., Ross, E. S., & Lear, S. A. (2015). Ethnic differences in cardiovascular disease risk factors: a systematic review of North American evidence. *Canadian Journal of Cardiology*, *31*, 1169-1179.

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.

Gill, K. F., Arthur, S. T., Swaine, I., Devereux, G. R., Huet, Y. M., Wikstrom, E., ... & Howden, R. (2015). Intensity-dependent reductions in resting blood pressure following short-term isometric exercise training. *Journal of Sports Sciences*, *33*, 616-621.

Go, A. S., Mozaffarian, D., Roger, V. L., Benjamin, E. J., Berry, J. D., Blaha, M. J., ...& Stroke, S. S. (2014). Heart disease and stroke statistics-2014 update: a report from the American Heart Association. *Circulation*, *129*, e28-e292.

Goldstein, D. S. (1983). Plasma catecholamines and essential hypertension. An analytical review. *Hypertension*, *5*, 86-99.

Gordan, R., Gwathmey, J. K., & Xie, L. H. (2015). Autonomic and endocrine control of cardiovascular function. *World Journal of Cardiology*, *7*, 204-214.

Graves, J. W., Nash, C., Burger, K., Bailey, K., & Sheps, S. G. (2003). Clinical decision-making in hypertension using an automated (BpTRU™) measurement device. *Journal of Human Hypertension*, *17*, 823-827.

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

Hall, J. E., Guyton, A. C., & Mizelle, H. L. (1989). Role of the renin-angiotensin system in control of sodium excretion and arterial pressure. *Acta Physiologica Scandinavica Supplementum*, *591*, 48-62.

Hart, E. C. J., & Charkoudian, N. (2014). Sympathetic neural regulation of blood pressure: influences of sex and aging. *Physiology*, *29*, 8-15.

Harvey, P. J., Morris, B. L., Kubo, T., Picton, P. E., Su, W. S., Notarius, C. F., & Floras, J. S. (2005). Hemodynamic after-effects of acute dynamic exercise in sedentary normotensive postmenopausal women. *Journal of Hypertension*, *23*, 285-292.

Harvey, A., Montezano, A. C., & Touyz, R. M. (2015). Vascular biology of ageing—Implications in hypertension. *Journal of Molecular and Cellular Cardiology*, *83*, 112-121.

Herd, J. A. (1970). Overall regulation of the circulation. *Annual Review of Physiology*, *101*, 289-312.

Holmes, C. L., Landry, D. W., & Granton, J. T. (2004). Science review: vasopressin and the cardiovascular system part 2-clinical physiology. *Critical Care London, 8*, 15-24.

Honzikova, N., & Fiser, B. (2009). Baroreflex sensitivity and essential hypertension in adolescents. *Physiological Research*, *58*, 605-612.

Howden, R., Lightfoot, J. T., Brown, S. J., & Swaine, I. L. (2002). The effects of isometric exercise training on resting blood pressure and orthostatic tolerance in humans. *Experimental Physiology*, *87*, 507-515.

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.

Joyner, M. J., & Limberg, J. K. (2014). Blood pressure regulation: every adaptation is an integration? *European Journal of Applied Physiology, 114,* 445-450.

Julius, S., Pascual, A. V., & London, R. (1971). Role of parasympathetic inhibition in the hyperkinetic type of borderline hypertension. *Circulation*, *44*, 413-418.

Julius, S., & Schork, M. A. (1978). Predictors of hypertension. *Annals of the New York Academy of Sciences*, *304*, 38-52.

Kahlmeier, S., Wijnhoven, T. M., Alpiger, P., Schweizer, C., Breda, J., & Martin, B. W. (2015). National physical activity recommendations: systematic overview and analysis of the situation in European countries. *BioMed Central Public Health*, *15*, 1-14.

Kearney, P. M., Whelton, M., Reynolds, K., Muntner, P., Whelton, P. K., & He, J. (2005). Global burden of hypertension: analysis of worldwide data. *The Lancet, 365,* 217-223.

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

Khan, N. A., Hemmelgarn, B., Padwal, R., Larochelle, P., Mahon, J. L., Lewanczuk, R. Z., ... & Schiffrin, E. L. (2007). The 2007 Canadian Hypertension Education Program recommendations for the management of hypertension: Part 2–therapy. *Canadian Journal of Cardiology*, *23*, 539-550.

Kilic-Erkek, O., Kilic-Toprak, E., Caliskan, S., Ekbic, Y., Akbudak, I. H., Kucukatay, V., & Bor-Kucukatay, M. (2016). Detraining reverses exercise-induced improvement in blood pressure associated with decrements of oxidative stress in various tissues in spontaneously hypertensive rats. *Molecular and Cellular Biochemistry*, *412*, 209-219.

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

Lawes, C. M., Vander Hoorn, S., & Rodgers, A. (2008). Global burden of blood-pressure-related disease, 2001. *The Lancet, 371,* 1513-1518.

Lawrence, M. M., Cooley, I. D., Huet, Y. M., Arthur, S. T., & Howden, R. (2015). Factors influencing isometric exercise training‐induced reductions in resting blood pressure. *Scandinavian Journal of Medicine & Science in Sports*, *25*, 131-142.

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

Leung, A. A., Nerenberg, K., Daskalopoulou, S. S., McBrien, K., Zarnke, K. B., Dasgupta, K., ... & Bolli, P. (2016). Hypertension Canada's 2016 Canadian 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. *The Lancet, 360*, 1903-1913.

Lindinger, M. I., & Sjogaard, G. (1991). Potassium regulation during exercise and recovery. *Sports Medicine*, *11*, 382-401.

Livada, R., & Shiloah, J. (2014). Calcium channel blocker-induced gingival enlargement. *Journal of Human Hypertension*, *28*, 10-14.

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. S. D. G., 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.

Mahabala, C., Kamath, P., Bhaskaran, U., Pai, N. D., & Pai, A. U. (2013). Antihypertensive therapy: nocturnal dippers and nondippers. Do we treat them differently? *Vascular Health and Risk Management*, *9*, 125-133.

Mancia, G., & Grassi, G. (2014). The autonomic nervous system and hypertension. *Circulation Research*, *114*, 1804-1814.

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

Maranon, R., & Reckelhoff, J. F. (2013). Sex and gender differences in control of blood pressure. *Clinical Science*, *125*, 311-318.

Mark, A. L. (1996). The sympathetic nervous system in hypertension: a potential long-term regulator of arterial pressure. *Journal of Hypertension. Supplement: Official Journal of the International Society of Hypertension*, *14*, 159-165.

Mayo, J. J., & Kravitz, L. (1999). A Review of the Acute Cardiovascular Responses to Resistance Exercise of Healthy Young and Older Adults. *The Journal of Strength & Conditioning Research*, *13*, 90-96.

McGowan, C. L**.** (2006a). Isometric Handgrip Training and Arterial Blood Pressure: Effects and Mechanisms (PhD Thesis). *Hamilton: McMaster University*.

McGowan, C. L., Visocchi, A., Faulkner, M., Verduyn, R., Rakobowchuk, M., Levy, A. S., ... & MacDonald, M. J. (2006b). Isometric handgrip training improves local flow-mediated dilation in medicated hypertensives. *European Journal of Applied Physiology*, *98*, 355-362.

McGowan, C. L., Levy, A. S., Mccartney, N., & Macdonald, M. J. (2007). Isometric handgrip training does not improve flow-mediated dilation in subjects with normal blood pressure. *Clinical Science*, *112*, 403-409.

Melo, C. M., Alencar Filho, A. C., Tinucci, T., Mion Jr, D., & Forjaz, C. L. (2006). Postexercise hypotension induced by low-intensity resistance exercise in hypertensive women receiving captopril. *Blood Pressure Monitoring*, *11*, 183-189.

Meredith, I. T., Jennings, G. L., Esler, M. D., Dewar, E. M., Bruce, A. M., Fazio, V. A., & Korner, P. I. (1990). Time-course of the antihypertensive and autonomic effects of regular endurance exercise in human subjects. *Journal of Hypertension*, *8*, 859-866.

Michel, M. C., Brodde, O. E., & Insel, P. A. (1990). Peripheral adrenergic receptors in hypertension. *Hypertension*, *16*, 107-120.

Michelini, L. C., O'Leary, D. S., Raven, P. B., & Nóbrega, A. C. (2015). Neural control of circulation and exercise: a translational approach disclosing interactions between central command, arterial baroreflex, and muscle metaboreflex. *American Journal of Physiology-Heart and Circulatory Physiology*, *309*, 381-392.

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

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

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

Millar, P. J., Levy, A. S., McGowan, C. L., McCartney, N., & MacDonald, M. J. (2013). Isometric handgrip training lowers blood pressure and increases heart rate complexity in medicated hypertensive patients. *Scandinavian Journal of Medicine & Science in Sports*, *23*, 620-626.

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

Modan, M., Halkin, H., Almog, S., Lusky, A., Eshkol, A., Shefi, M., ... & Fuchs, Z. (1985). Hyperinsulinemia. A link between hypertension obesity and glucose intolerance. *Journal of Clinical Investigation*, *75*, 809-817.

Moraes, M. R., Bacurau, R. F., Casarini, D. E., Jara, Z. P., Ronchi, F. A., Almeida, S. S., ... & Barros, C. C. (2012). Chronic conventional resistance exercise reduces blood pressure in stage 1 hypertensive men. *The Journal of Strength & Conditioning Research*, *26*, 1122-1129.

Murphy, M. N., Mizuno, M., Mitchell, J. H., & Smith, S. A. (2011). Cardiovascular regulation by skeletal muscle reflexes in health and disease. *American Journal of Physiology-Heart and Circulatory Physiology, 301,* 1191-1204.

Murray, A., Delaney, T., & Bell, C. (2006). Rapid onset and offset of circulatory adaptations to exercise training in men. *Journal of Human Hypertension*, *20*, 193-200.

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 angiotensin II production and cellular responses to renin. *Journal of Clinical Investigation, 190,* 1417-1427.

Nielsen, S., Chou, C. L., Marples, D., Christensen, E. I., Kishore, B. K., & Knepper, M. A. (1995). Vasopressin increases water permeability of kidney collecting duct by inducing translocation of aquaporin-CD water channels to plasma membrane. *Proceedings of the National Academy of Sciences*, *92*, 1013-1017.

O'Brien, E., Beevers, G., & Lip, G. Y. (2001). Blood pressure measurement: Part III-Automated sphygmomanometry: ambulatory 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*, 11-18.

O'Driscoll, J. M., Taylor, K. A., Wiles, J. D., Coleman, D. A., & Sharma, R. (2017). Acute cardiac functional and mechanical responses to isometric exercise in prehypertensive males. *Physiological Reports*, *5*, e13236.

Ogedegbe, G., & Pickering, T. (2010). Principles and techniques of blood pressure measurement. *Cardiology Clinics*, *28*, 571-586.

Olher, R. D. R. V., Bocalini, D. S., Bacurau, R. F., Rodriguez, D., Figueira Jr, A., Pontes Jr, F. L., ... & Moraes, M. R. (2013). Isometric handgrip does not elicit cardiovascular overload or post-exercise hypotension in hypertensive older women. *Clinical Interventions in Aging*, *8*, 649.

Ontario Ministry of Health and Long-Term Care (2012). Ontario Programs for Health Promotion and Disease Prevention. Retrieved from: http://www.phac-aspc.gc.ca/cd-mc/cvd-mcv/funded-projects-subventionnes-eng.php

O'Regan, R. G., & Majcherczyk, S. (1982). Role of peripheral chemoreceptors and central chemosensitivity in the regulation of respiration and circulation. *Journal of Experimental Biology*, *100*, 23-40.

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.

Panza, J. A., Epstein, S. E., & Quyyumi, A. A. (1991). Circadian variation in vascular tone and its relation to α-sympathetic vasoconstrictor activity. *New England Journal of Medicine*, *325*, 986-990.

Peixoto, A. J., & White, W. B. (2007). Circadian blood pressure: clinical implications based on the pathophysiology of its variability. *Kidney International*, *71*, 855-860.

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

Pickering, T. G., Hall, J. E., Appel, L. J., Falkner, B. E., Graves, J., Hill, M. N., ... & Roccella, E. J. (2005). Recommendations for blood pressure measurement in humans and experimental animals. *Circulation*, *111*, 697-716.

Pickering, T. G., Shimbo, D., & Haas, D. (2006). Ambulatory blood-pressure monitoring. *New England Journal of Medicine*, *354*, 2368-2374.

Potter, L. R., Yoder, A. R., Flora, D. R., Antos, L. K., & Dickey, D. M. (2009). Natriuretic peptides: their structures, receptors, physiologic functions and therapeutic applications. *cGMP: Generators, Effectors and Therapeutic Implications, 191,* 341-366.

Pollock, D.M., Keith, T.L., & Highsmith, R.F. (1995). Endothelin receptors and calcium signalling. *The Federation of American Societies for Experimental Biology Journal, 9,* 1196-1204.

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

Queiroz, A. C. C., Kanegusuku, H., & Forjaz, C. L. D. M. (2010). Effects of resistance training on blood pressure in the elderly. *Arquivos Brasileiros de Cardiologia*, *95*, 135-140.

Raven, P. B., & Chapleau, M. W. (2014). Blood pressure regulation XI: overview and future research directions. *European Journal of Applied Physiology, 114*, 579-586.

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

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

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

Sever, P. S., & Poulter, N. R. (1989). A hypothesis for the pathogenesis of essential hypertension: the initiating factors. *Journal of Hypertension*, *7*, 9-12.

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

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.

Singh, J. P., Larson, M. G., Tsuji, H., Evans, J. C., O'Donnell, C. J., & Levy, D. (1998). Reduced heart rate variability and new-onset hypertension. *Hypertension*, *32*, 293-297.

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.* Paper 5285.

Somani, Y., 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.

Somers, V. K., Conway, J., Johnston, J., & Sleight, P. (1991). Effects of endurance training on baroreflex sensitivity and blood pressure in borderline hypertension. *The Lancet*, *337*, 1363-1368.

Sowers, J. R. (2013). Diabetes mellitus and vascular disease. *Hypertension*, *61*, 943-947.

SPRINT Research Group. (2015). A randomized trial of intensive versus standard blood-pressure control. *New England Journal of Medicine*, *2015*, 2103-2116.

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

Statistics Canada. (2015a). The 10 Leading Causes of Death, 2012. Retrieved from: http://www.statcan.gc.ca/pub/82-625-x/2015001/article/14296-eng.htm

Statistics Canada. (2015b). Estimates of population, by age group and sex for July 1, Canada, provinces and territories. Retrieved from: http://www5.statcan.gc.ca/cansim/a26?lang=eng&retrLang=eng&id=0510001&&pattern=&stByVal=1&p1=1&p2=31&tabMode=dataTable&csid=

Statistics Canada. (2015c). Fruit and vegetable consumption, 2014. Retrieved from: http://www.statcan.gc.ca/pub/82-625-x/2015001/article/14182-eng.htm

Stiller-Moldovan, C., Kenno, K., & McGowan, C.L. (2012). 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.

Sweitzer, N. K. (2003). What is an angiotensin converting enzyme inhibitor? *Circulation*, *108*, e16-e18.

Sztajzel, J. (2004). Heart rate variability: a noninvasive electrocardiographic method to measure the autonomic nervous system. *Swiss Medical Weekly*, *134*, 514-522.

Taylor, A. C., McCartney, N. E. I. L., 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.

Thompson, P. D., Arena, R., Riebe, D., & Pescatello, L. S. (2013). ACSM's new preparticipation health screening recommendations from ACSM's guidelines for exercise testing and prescription. *Current Sports Medicine Reports, 12*, 215-217.

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

Tremblay, M. S., Warburton, D. E., Janssen, I., Paterson, D. H., Latimer, A. E., Rhodes, R. E., ... & Murumets, K. (2011). New Canadian physical activity guidelines. *Applied Physiology, Nutrition, and Metabolism*, *36*, 36-46.

Turner, J. R., Viera, A. J., & Shimbo, D. (2015). Ambulatory blood pressure monitoring in clinical practice: a review. *The American Journal of Medicine*, *128*, 14-20.

Van Hoof, R., Macor, F., Lijnen, P., Staessen, J., Thijs, L., Vanhees, L., & Fagard, R. (1996). Effect of strength training on blood pressure measured in various conditions in sedentary men. *International Journal of Sports Medicine*, *17*, 415-422.

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.

Wang, T. J., & Vasan, R. S. (2005). Epidemiology of uncontrolled hypertension in the United States. *Circulation*, *112*, 1651-1662.

Wang, M., Monticone, R. E., & Lakatta, E. G. (2010). Arterial aging: a journey into subclinical arterial disease. *Current Opinion in Nephrology and Hypertension*, *19*, 201-207.

Weippert, M., Behrens, K., Rieger, A., Stoll, R., & Kreuzfeld, S. (2013). Heart rate variability and blood pressure during dynamic and static exercise at similar heart rate levels. *PLoS One*, *8*, e83690.

Wiles, J. D., Allum, S. R., Coleman, D. A., & Swaine, I. L. (2008). The relationships between exercise intensity, heart rate, and blood pressure during an incremental isometric exercise test. *Journal of Sports Sciences*, *26*, 155-162.

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

Wilkins K., Campbell, N. R., Joffres, M. R., McAlister, F. A., Nichol, M., Quach, S., Johansen, H. L., & Tremblay, M. S. (2010). Blood pressure in Canadian adults. *Statistics Canada Health Reports, 21,* 37-46.

Windsor-Essex County Health Unit. (2017). High Blood Pressure in Windsor-Essex County. Retrieved from: https://www.wechu.org/reports/high-blood-pressure-windsor-essex-county

World Health Organization. (2013) A global brief on hypertension; silent killer, global public health crisis. Retrieved from: http://apps.who.int/iris/bitstream/10665/79059/1/WHO_DCO_WHD_2013.2_eng.pdf?ua=1

World Health Organization (2017). Cardiovascular Diseases. Retrieved from: http://www.who.int/mediacentre/factsheets/fs317/en/

Zanettini, R., Bettega, D., Agostoni, O., Ballestra, B., Del Rosso, G., Di Michele, R., & Mannucci, P. M. (1997). Exercise training in mild hypertension: effects on blood pressure, left ventricular mass and coagulation factor VII and fibrinogen. *Cardiology*, *88*, 468-473.

Zheng, L., Sun, Z., Li, J., Zhang, R., Zhang, X., Liu, S., ... & Sun, Y. (2008). Pulse pressure and mean arterial pressure in relation to ischemic stroke among patients with uncontrolled hypertension in rural areas of China. *Stroke*, *39*, 1932-1937.

Chapter 2: Application of Isometric Resistance Training to Treat Hypertension

2.1 Introduction

Cardiovascular disease (CVD) refers to all disorders of the heart and circulatory system that interfere with efficient functioning (Go et al., 2014). CVD is the leading cause of death globally, representing 31% of deaths in 2012 (WHO, 2017), and 29% of Canadian deaths in the year 2008 (Statistics Canada, 2015a). It is estimated that by the year 2030, CVD will be responsible for 23 million deaths worldwide (WHO, 2017). Hypertension (HTN), or high blood pressure (BP) is a major prognostic risk factor for the development of CVD and has been deemed a global health crisis by the World Health Organization (WHO) (WHO, 2013). In Canada, 1 in 5 people have HTN, and it is the number one reason why adults visit their health care provider (Wilkins et al., 2010; Hemmelgarn et al., 2008). In Windsor-Essex County, 27% of individuals aged 45-64 years and 48% of individuals aged 65 years and older were reported to have high BP in 2012 (Windsor-Essex County Health Unit, 2017). Upwards of 50% of individuals treated for HTN in Canada and the United States are not controlled to clinical targets, putting these individuals at even greater risk of hypertensive complications (Wilkins et al., 2010; Chobanian et al., 2003). Taken together, it is not surprising that the WHO now considers the early prevention and treatment of HTN key global priorities (WHO, 2017).

Meta-regression analyses have shown that a reduction of 5 mmHg in SBP can reduce the risk of coronary heart disease by 8%, stroke by 13%, heart failure by 14%, and all-cause mortality by 6% (Ettehad et al., 2016). Current treatment and prevention interventions for BP control include lifestyle modifications and pharmacotherapy, with dietary modifications and increased physical activity as important components (Khan et al., 2007; Brook et al., 2013). In spite of the proven benefits of exercise in controlling BP,

only 1 in 5 Canadians are meeting physical exercise guidelines (Statistics Canada, 2015b). Common barriers for those who do not exercise include lack of time and/or energy (Ebben & Brudzynski, 2008). In addition, antihypertensive medication is not always an effective solution for everyone (Colley et al., 2011). The poor adherence and/or lack of responsiveness to traditional treatment require the need for novel and effective BP-lowering treatments.

One such intervention is isometric handgrip (IHG) training, a novel form of isometric resistance training (IRT) recently endorsed by the American Heart Association (Brook et al., 2013) and Hypertension Canada (Leung et al., 2016), consisting of four, 2-minute sustained bilateral handgrip contractions at 30% of maximum voluntary contraction (MVC) conducted 3-5 times per week for 8-10 weeks. Numerous small-scale proof-of-concept studies have provided evidence for the BP-lowering effectiveness of this simple and non-time consuming intervention in a variety of populations, including men and women, normotensive and hypertensive individuals, and those medicated for HTN (Inder et al., 2016; Millar et al., 2014). The most recent meta-analysis of IRT reported mean reductions of resting systolic BP (SBP) and diastolic BP (DBP) of 5/4 mmHg, respectively (Inder, et al., 2016). Millar and colleagues (2014) have also reported that there is a strong correlation between the magnitude of change following IRT and baseline BP, such that the greatest reductions are observed in those with higher pre-training BP.

Ambulatory BP monitoring is now widely recognized as superior to resting automated office BP (AOBP) measures for its prognostic and diagnostic ability in clinical care (Pickering, 2006; Leung et al., 2016). For example, the dipping pattern (change in

BP from daytime to nighttime measures) available with the use of ambulatory BP monitoring has become an increasingly important prognostic parameter for CVD risk (O'Brien et al., 2001; Boggia et al., 2011). This dipping pattern can be used to monitor treatment after initiation and determine the efficacy of antihypertensive therapies (Mahabala et al., 2013). However, the effects of IRT on ambulatory BP have been minimally investigated. In the only published trials to date, significant post-training reductions in mean 24-hour SBP were observed in young healthy adults (Somani et al., 2017), while clinically relevant reductions were noted in a well-controlled HTN cohort (Stiller-Moldovan et al., 2012) following IHG training interventions.

Many healthcare professionals turn immediately to pharmaceutical treatments of HTN, primarily because adherence to dietary and exercise strategies is so poor (Carlson et al., 2014; Brook et al., 2013). With respect to the latter, the relatively short sessions required for IHG training and the ability to train anywhere are advantages that may produce greater exercise adherence in comparison to traditional aerobic or dynamic resistance training (Carlson et al., 2014). Moreover, seeing as the only cost is the actual purchase of the handgrip dynamometer, IHG training has the potential to be significantly more cost-effective over a lifetime in comparison to antihypertensive medication (Carlson et al., 2014).

As with many BP-lowering methods, IHG training is particularly effective in individuals with higher pre-training resting BP values (including medicated hypertensives), as noted above, and in those ≥45 years of age (Inder et al., 2016). Moreover, normotensive and hypertensive individuals with high pre-training SBP reactivity to cardiovascular stress tasks (e.g., simple math task; 2-minute IHG task) also

appear highly responsive to IHG training (Millar et al., 2009; Badrov et al., 2013; Somani, 2015). In other words, those with greater increases in SBP during the acute stress task have the greatest reductions in resting SBP with IRT. The predictive effects were not carried over to ambulatory BP reductions in normotensive individuals (Somani et al., 2017). Cardiovascular reactivity as a predictor of IHG training effectiveness to ambulatory BP has yet to be investigated in hypertensive individuals. This highlights the need to explore the cardiovascular reactivity to ambulatory BP in this population, since a simple cardiovascular stress task may help clinicians identify those who will respond to IHG training with a reduction in resting and ambulatory BP.

Gaining insight into the optimal training frequency/duration needed to sustain the effects of IRT has significant clinical applicability, as does gaining insight into the tolerability of the intervention from a patient perspective over the long-term. With respect to training cessation, studies by Howden et al. (2002) and Devereux et al. (2010) found that reductions in SBP (means of 5-12 mmHg) in the normotensive population were lost after only 7-10 days of detraining. However, the exercise intervention for each study was only 5 weeks and 4 weeks, respectively. On the contrary, McGowan (2006a) found that the SBP reductions after 8 weeks of IHG training were maintained following 8 weeks of training cessation in medicated hypertensives. These findings must be interpreted with caution because of the small sample sizes. The effect of detraining following IRT on ambulatory BP has yet to be explored, and no study to date has attempted to gain insight into IRT as a feasible and sustainable BP-lowering intervention over the long-term from a patient perspective.

2.2 Purpose and Hypotheses

The purpose of this prospective investigation was to fill gaps in the current IRT literature by addressing the following in a poorly controlled medicated hypertensive population:

1. To investigate the concomitant BP-lowering effects of 8 weeks of IHG training on resting and ambulatory BP.
2. To explore the effect of 4 weeks of training cessation on resting and ambulatory BP.
3. To determine if SBP reactivity to an IHG task could predict IHG training-induced reductions in resting and ambulatory BP.
4. To gain knowledge about the feasibility of IHG training as a long-term BP-lowering treatment from a patient perspective.

It was hypothesized that:

1. 8 weeks of IHG training would elicit concomitant reductions in resting and ambulatory BP.
2. A detraining period of 4 weeks following 8 weeks of IHG training would cause resting and ambulatory BP to return to near pre-training values.
3. SBP reactivity to an IHG task at baseline would be predictive of IHG responsiveness, such that participants who responded to the IHG task with the greatest increases in SBP would experience the greatest reductions in resting and ambulatory BP.
4. IHG will be well received as a long-term BP-lowering tool.

2.3 Methods

Study Participants

Individuals with Stage 1 HTN with treated resting automated office BP (AOBP) above the normal range (120-159/80-99 mmHg) were recruited from Windsor, Ontario, Canada and surrounding communities (Appendix A). Participants were excluded if they had any hospitalization within the last 3 months, any medication change within the last 2 months or over the course of the intervention period, a planned absence or vacation lasting longer than 1 week, BP readings rising into Stage 2 HTN, secondary HTN, lack of primary care provider support, and/or physical limitations that would impair exercise performance. The University of Windsor Research Ethics Board approved the study (Appendix B, C, D), and all participants provided written informed consent prior to participation, as well as ongoing consent throughout the entirety of the intervention.

Eligibility and Familiarization

Visit 1

Individuals who expressed interest in the study met study investigators in the Physical Activity and Cardiovascular Research Laboratory (PACR Lab – HK 240, University of Windsor, Windsor, ON, Canada). Following explanation of all parts of the study, medical history was obtained via a brief questionnaire in consented participants (Appendix E). Any questions or concerns regarding the study were answered, and participants were informed of their right to withdraw at any time. Next, resting BP and heart rate (HR) were measured using standard laboratory protocol following 10 minutes of seated rest with an automated brachial artery oscillometric device (Ogedegbe & Pickering, 2010; Dinamap Carescape v100, Critikon, Tampa, Florida, USA; Appendix F).

In brief, a cuff was placed around the upper dominant arm and inflated to a pressure greater than the SBP in order to occlude the brachial artery (Badrov et al., 2013). Four measures were obtained, with 2-minute rest intervals between each measure. The first measure was discarded and the final three measures averaged to assess eligibility. If participants met the resting BP threshold, Visit 2 was scheduled.

Visit 2

At least 24 hours following Visit 1, potential participants returned to the PACR Lab. The second visit began by measuring resting BP and HR as previously described (see Section: Visit 1). If the average resting AOBP values from Visits 1 and 2 were between 120-159/80-99 mmHg, participants underwent a familiarization session during which the participant was able to experience all techniques employed during the investigation. This served to habituate participants to the testing protocol and minimize the effects of anxiety or unfamiliarity on testing variables. At the completion of Visit 2, individuals were provided with a physical activity readiness medical examination (PARmed-X; Appendix G) to be completed by their health care provider (e.g. physician or nurse practitioner). This document also asked the health care provider if the participant had primary or secondary HTN. In addition, all participants received two letters for their health care provider:

- a notification of the participant's involvement in the study and;
- an acknowledgement of this participation to be signed by the participant's health care provider (Appendix H).

Health care provider support was the final requirement for study eligibility.

Testing

Upon establishment of eligibility, baseline testing occurred to assess AOBP. All testing was conducted in a quiet, temperature-controlled room (20°C - 23°C) following a 24-hour abstinence from alcohol consumption and vigorous activity, a 12-hour abstinence from caffeine, 4 hours post-prandial, and with a voided bladder (Somani et al., 2017). Testing was repeated at the same time of day following 8 and 12 weeks. On each testing day, resting AOBP and HR were assessed as described previously (see Section: Visit 1). On the baseline-testing day only, participants conducted a 2-minute bout on an IHG (2 minutes at 30% of their maximum voluntary contraction (MVC); ZonaPLUS, Zona HEALTH, Boise, Idaho, USA; Appendix I.), referred to as the IHG task. During the 2-minute bout, BP and HR measurements were recorded at 40 seconds, 80 seconds, and 120 seconds during the task and averaged to assess cardiovascular reactivity (Gerin et al., 2000). On the 12-week testing day only, participants completed an exit feasibility scan (Appendix J). Participants completed the scan seated at a table, in isolation with a pen and paper.

At the conclusion of each laboratory testing session (baseline, after week 8, after week 12), participants were fitted with a 24-hour ambulatory BP monitor (SpaceLabs 90207 Ambulatory Blood Pressure Monitor, SpaceLabs Inc., Redmond, Washington, USA; Appendix K). For 24 hours, BP was measured and recorded every half hour during waking hours (6 AM to 10 PM) and every hour during nighttime hours (10 PM to 6 AM) (Stiller-Moldovan et al., 2012; Somani et al., 2017). In order to ensure standardization of diet and activities during pre-IHG training, post-IHG training, and post-IHG detraining, participant diet and activities during the 24-hour period were recorded and discussed with

participants (Appendix L). This diet and activity level was revisited and encouraged during the post-IHG training and post-IHG detraining measure of ambulatory BP (Stiller-Moldovan et al., 2012; Somani et al., 2017).

Training

Participants trained on the IHG 3 times per week for 8 weeks using the traditional protocol, whereby four sets of 2-minute IHG contractions were performed on a programmed handgrip dynamometer at 30% of MVC using alternate hands, with each contraction separated by a 1 minute rest period (Badrov et al., 2013; Carlson et al., 2014). An exercise trainer in the PACR Laboratory supervised two training sessions per week, while the third session was completed in the participant's home. Participants were provided detailed written instructions on how to complete the IHG exercise to ensure proper at-home training and completed training log books, in which the date of exercise completion, MVC scores for each training session, and final compliance scores were recorded (Appendix M). To ensure participant safety and preparedness for isometric exercise, resting BP and HR were measured (see Section: Visit 1) prior to each training session (this data was not used for analysis). Any changes in exercise, diet, supplements, and medication were recorded in the log book, and were discussed with participants at each laboratory visit to ensure these potentially confounding variables remained unchanged throughout the 12-week intervention period (Appendix N). Participants also signed the logbook at each visit to ensure ongoing consent, and HTN-related health care provider visits were recorded. A registered nurse monitored the BP and HR measurements over the course of the study, as well as participant's medical history to ensure safety.

Following the 8 weeks of training, participants ceased training for a 4-week period. Participants still came into the PACR Lab two times per week to have their resting AOBP and HR measured (see Section: Visit 1), and any changes in diet, exercise, supplements, or medication were discussed.

Statistical Analysis

Dependent t-tests were used to examine the training and detraining effects of IHG training on resting AOBP (SBP, DBP, MAP), ambulatory BP (24-hour, daytime and nighttime), as well as resting and ambulatory HR. Therefore, time was the independent variable and BP and HR were the dependent variables. In regard to the ambulatory data analysis, any BP measure greater than 2 standard deviations away from the daytime or nighttime mean (given the time of the measurement) was omitted (Staessen et al., 1991). Post-hoc repeated measures ANOVA were used to determine power for all significant resting and 24-hour ambulatory BP changes.

Cardiovascular reactivity (SBP, DBP, and HR responses) to the IHG task was calculated as the difference between the average IHG task-induced values and the mean baseline testing values (Gerin et al., 2000). To determine the relationship between cardiovascular reactivity and IHG training effects, Pearson correlation coefficients between the cardiovascular reactivity values and the residualized IHG SBP change were assessed. Since pre-training resting BP and the magnitude of BP reduction following IHG training are correlated (Millar et al., 2007), residualized changes in SBP were used, and were obtained by regressing pre-post training changes in SBP on pre-training SBP. The regression analysis was performed for both resting and ambulatory SBP. Bivariate correlation was used to determine the relationship between pre-IHG training resting SBP

and the change in resting SBP following 8 weeks of IHG training.

Repeated measures ANOVA were used to determine the change in average MVC per training session over the IHG training period. All data were analyzed using IBM SPSS Statistics 23 software (SPSS Inc., Chicago, Illinois, USA) and statistical significance was determined at $P \leq 0.05$. See Appendix O for Statistical Analysis.

2.4 Results

Participant Baseline Characteristics

Of the 6 individuals recruited, 4 were deemed eligible to participate. Participant baseline characteristics are displayed in Table 1. All 4 participants trained for 8 weeks and completed 24 IHG sessions. Compliance to maintaining 30% MVC throughout IHG bouts was 97%, while the average MVC was 61 (in equipment units). No changes in MVC were observed over the training period ($P > 0.05$). There were no reported changes in exercise, diet, or medication throughout the intervention period.

Table 1. Participant baseline characteristics

Characteristics	Participants (n = 4)
Women	2
Age (years)	58 ± 2
Height (cm)	168 ± 5
Weight (kg)	74 ± 6
BMI (kg/m^2)	27 ± 3
Resting SBP (mmHg)	134 ± 14
Resting DBP (mmHg)	77 ± 10
Resting MAP (mmHg)	96 ± 11
Resting HR (beats/minute)	60 ± 5
Ambulatory Measures	
24-hour SBP (mmHg)	135 ± 14
24-hour DBP (mmHg)	83 ± 9
24-hour MAP (mmHg)	101 ± 8
24-hour HR (beats/min)	64 ± 4
Medication Classification:	
Calcium channel blocker	1
ACE Inhibitor + Calcium channel blocker	1
ACE Inhibitor + β-blocker	1
Diuretic	1

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; ACE, angiotensin converting enzyme. Values are mean ± SD.

Effects of Isometric Handgrip Training and Detraining on Resting Blood Pressure and Heart Rate

Following 8 weeks of IHG training, resting SBP ($P = 0.352$), DBP ($P = 0.787$), MAP ($P = 0.731$), and HR ($P = 0.792$) remained unchanged (see Table 2). The relationship between pre-training IHG resting SBP and the change in SBP following IHG training is shown in Figure 1 ($r = -0.904$, $P = 0.096$). A 4-week cessation post-IHG

training resulted in no changes in resting SBP ($P = 0.513$), DBP ($P = 0.127$), MAP ($P = 0.242$), and HR ($P = 0.639$) between post-IHG training and post-IHG detraining (see Table 2). Additionally, resting SBP, DBP, MAP, and HR remained unchanged from pre-IHG training to post-IHG detraining (all $P > 0.05$, see Table 2). Individual changes in resting SBP, DBP, and MAP over the time course of the study are shown in Figure 2.

Table 2. Resting cardiovascular adaptations to isometric handgrip training and detraining

	Participants (n = 4)		
	Pre-IHG Training	**Post-IHG Training**	**Post-IHG Detraining**
Resting SBP (mmHg)	134 ± 14	128 ± 7	123 ± 15
Resting DBP (mmHg)	77 ± 10	78 ± 5	70 ± 5
Resting MAP (mmHg)	96 ± 11	95 ± 5	88 ± 8
Resting HR (beats/minute)	60 ± 5	60 ± 3	59 ± 2

IHG, isometric handgrip; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate. Values are mean ± SD; all $P > 0.05$.

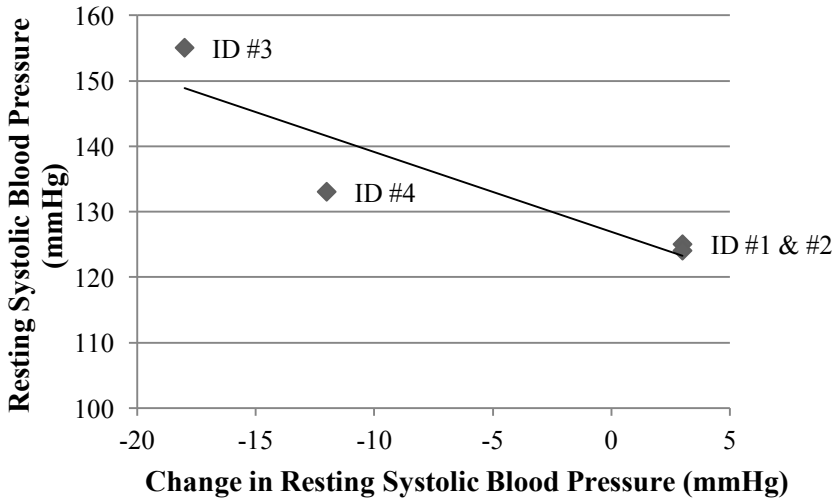
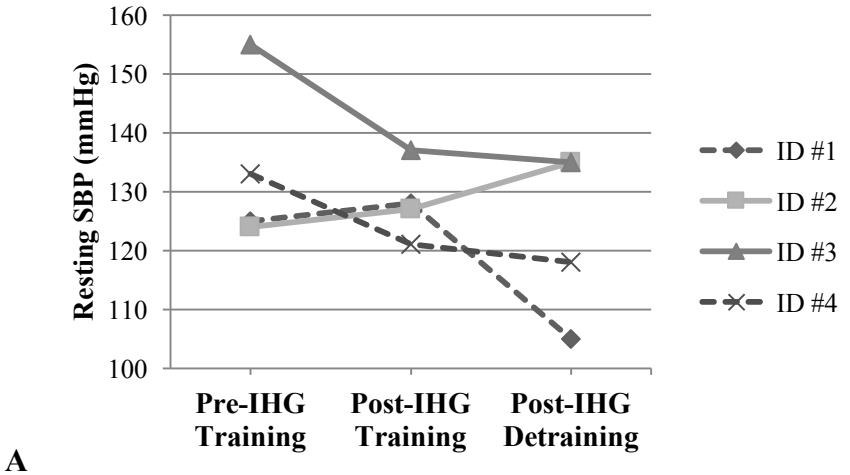
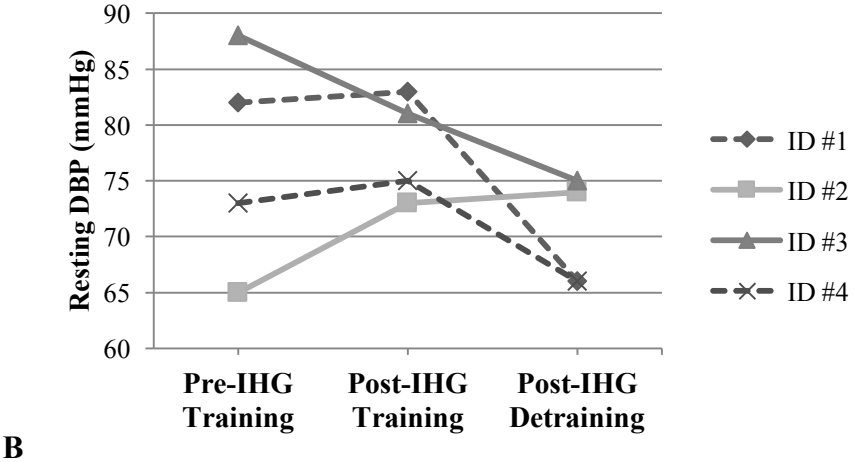


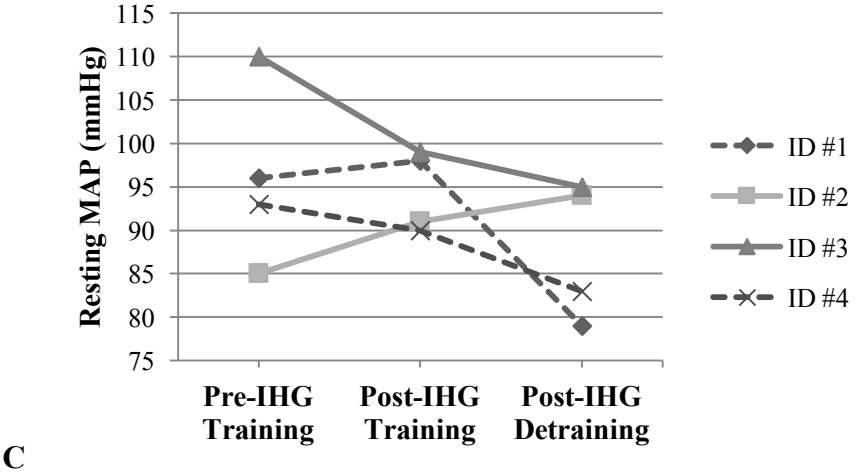
Figure 1. Relationship of pre-IHG training resting SBP and the change in resting systolic blood pressure (SBP) after isometric handgrip (IHG) training; $r = -0.904$, $P = 0.096$.



A



B



C

Figure 2. The effect of isometric handgrip (IHG) training and detraining on resting (A) systolic blood pressure (SBP), (B) diastolic blood pressure (DBP), and (C) mean arterial pressure (MAP); all $P > 0.05$.

Effects of Isometric Handgrip Training and Detraining on Ambulatory Blood Pressure, Heart Rate and Dipping Status

After 8 weeks of IHG training, 24-hour, daytime, and nighttime ambulatory SBP, DBP, MAP, and HR, as well as dipping, remained unchanged (all $P > 0.05$, see Table 3). A detraining period of 4 weeks directly following 8 weeks of IHG training resulted in no changes in 24-hour, daytime, and nighttime ambulatory SBP, DBP, MAP, and HR between post-IHG training and post-IHG detraining (all $P > 0.05$, see Table 3). In contrast, there was a statistically significant reduction in daytime ambulatory MAP from pre-IHG training to post-IHG detraining ($P = 0.022$). Excluding daytime MAP, 24-hour, daytime, and nighttime ambulatory SBP, DBP, MAP, and HR between pre-IHG training and post-IHG detraining remained unchanged (all $P > 0.05$, see Table 3). Individual changes in 24-hour, daytime, and nighttime ambulatory SBP over the time course of the study are shown in Figure 3.

Table 3. Ambulatory cardiovascular adaptations to isometric handgrip training and detraining

	Participants (n = 4)		
	Pre-IHG Training	**Post-IHG Training**	**Post-IHG Detraining**
24-hour Ambulatory BP			
SBP (mmHg)	135 ± 14	133 ± 9	128 ± 9
DBP (mmHg)	83 ± 9	83 ± 5	78 ± 4
MAP (mmHg)	101 ± 8	100 ± 6	95 ± 6
HR (beats/minute)	64 ± 4	63 ± 5	61 ± 5
Daytime Ambulatory BP			
SBP (mmHg)	138 ± 13	137 ± 8	132 ± 10
DBP (mmHg)	87 ± 7	86 ± 5	82 ± 5
MAP (mmHg)	105 ± 6	103 ± 6	99 ± 7*
HR (beats/minute)	65 ± 5	63 ± 4	62 ± 6
Nighttime Ambulatory BP			
SBP (mmHg)	125 ± 18	120 ± 12	115 ± 10
DBP (mmHg)	72 ± 13	71 ± 7	67 ± 4
MAP (mmHg)	90 ± 14	88 ± 8	84 ± 5
HR (beats/minute)	60 ± 5	60 ± 5	57 ± 3
Dipping			
SBP (%)	10 ± 5	13 ± 6	13 ± 3
DBP (%)	17 ± 8	17 ± 6	18 ± 1
MAP (%)	14 ± 8	14 ± 6	15 ± 3

IHG, isometric handgrip, SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate. Values are mean ± SD. *Significantly different from pre-IHG training; all $P < 0.05$.

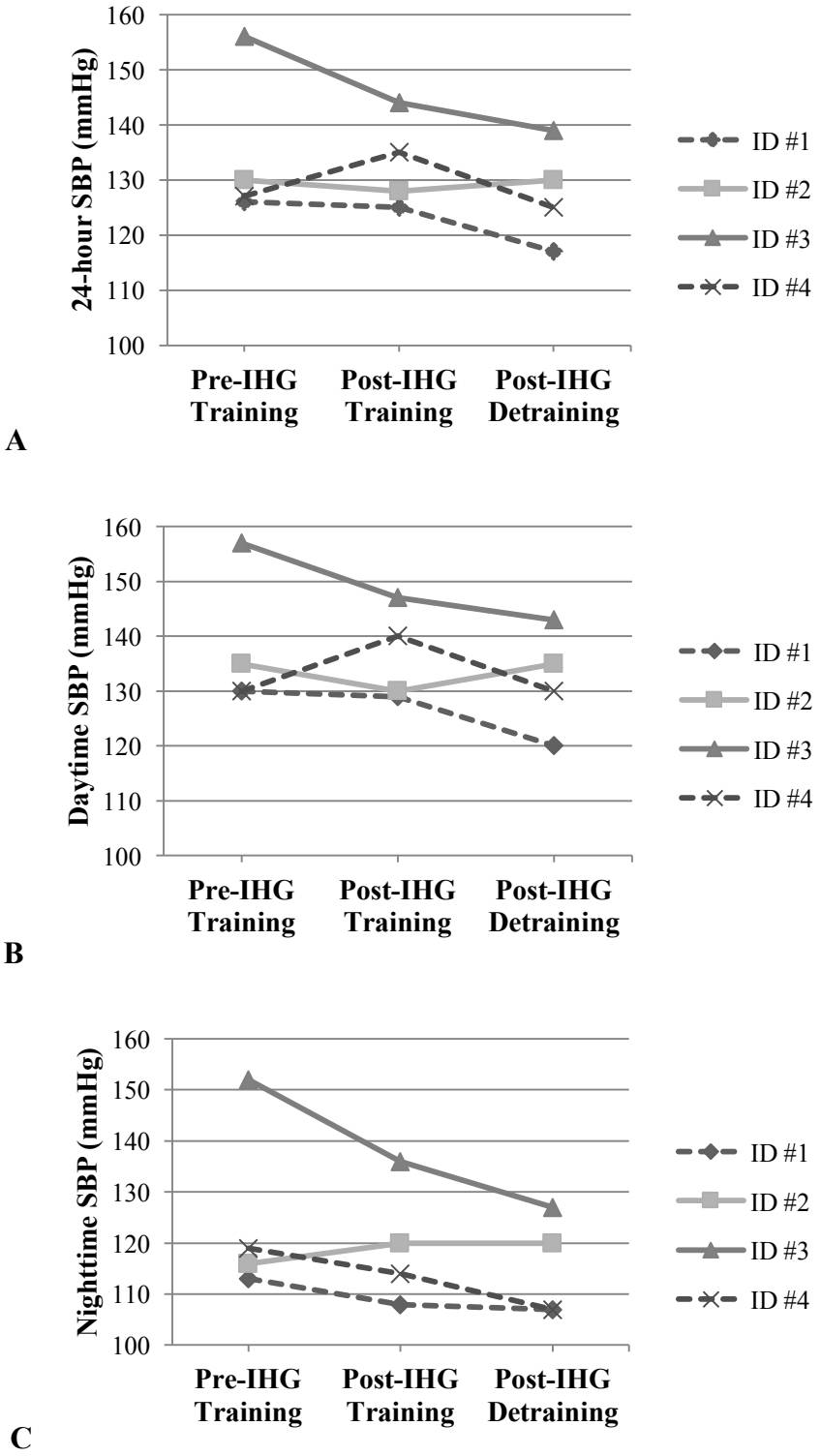


Figure 3. The effect of isometric handgrip (IHG) training and detraining on (A) 24-hour, (B) daytime, and (C) nighttime ambulatory systolic blood pressure (SBP); all $P > 0.05$.

Cardiovascular Reactivity as a Predictor of Isometric Handgrip Training Effectiveness

Cardiovascular stress reactivity responses to the IHGT at baseline and the relationship to IHG training effects are displayed in Table 4. No associations were observed between the reactivity of SBP, DBP, and HR to the IHG task and the residualized changes in resting SBP (all $P > 0.05$). Furthermore, no association was observed between any measure of cardiovascular reactivity to the IHG task and training-induced reductions in 24-hour, daytime, and nighttime ambulatory SBP (all $P > 0.05$).

Table 4. Baseline cardiovascular stress reactivity and the relationship to isometric handgrip training adaptations

	ΔSBP (mmHg)	***r***	***P***	**ΔDBP (mmHg)**	***r***	***P***	**ΔHR (bpm)**	***r***	***P***
IHGT	19 ± 9	0.584	0.416	11 ± 6	0.705	0.295	5 ± 3	0.456	0.544

IHGT, isometric handgrip task; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; bpm, beats per minute. Values are mean ± SD.

Participant's Perception of Isometric Handgrip Training

Following the completion of the study, participants were asked to complete 9 questions regarding their experience with IHG training. The results are presented in Table 5. It is worth highlighting that all participants (n = 4) strongly agreed with the statements regarding IHG training, "I found that training 3 times per week was manageable" and "If the option was available, I would continue to train".

Table 5. Participant's perception of isometric handgrip training

	Participant (n = 4) Response Frequency:				
Statement:	**Strongly Disagree**	**Disagree**	**Undecided**	**Agree**	**Strongly Agree**
1. I enjoyed handgrip training.	0	0	0	2	2
2. I found handgrip training challenging.	0	1	1	2	0
3. I found that training 3 times per week was manageable.	0	0	0	0	4
4. I felt it was difficult finding the time to train.	3	1	0	0	0
5. If the option were available, I would continue to train.	0	0	0	0	4
6. I would be willing to pay for the current cost of a handgrip (approximately $600.00).	0	0	3	1	0
7. I felt better after handgrip training for 8 weeks.	0	0	0	2	2
8. I believe that my health has improved after handgrip training for 8 weeks.	0	0	0	3	1
9. I would recommend handgrip training to others.	0	0	0	2	2

2.5 Discussion

The present study is the first to investigate the cardiovascular reactivity to a stress task in order to predict changes in ambulatory BP following 8 weeks of IHG training. Additionally, findings from the exit scan have provided valuable insight into participant's perspective about IRT in order to guide future studies.

Effects of Isometric Handgrip Training and Detraining on Resting and Ambulatory Blood Pressure

Contrary to hypothesis 1, 8 weeks of IHG training did not elicit a statistically significant reduction in resting or ambulatory BP. With respect to resting BP, our findings are in disagreement with previous studies examining the effects of IHG on medicated hypertensives with borderline to uncontrolled HTN (McGowan et al., 2006b; Millar et al., 2013; Badrov et al., 2013). One possible reason for this discrepancy in the effectiveness of IHG training to reduce resting BP in medicated hypertensives is that each participant was on a different anti-hypertensive medication or a different combination of medications. There is limited information on the interaction each medication has with exercise, but given the fact that each medication reduces BP through a different physiological pathway, it can be speculated that the type of medication can influence the BP lowering changes resulting from exercise. Additionally, there is substantial inter-participant variability when assessing BP changes over the 8-week intervention. As shown in Figure 2, participants #3 and #4 had a reduction of 18 mmHg and 12 mmHg in resting SBP, respectively. These reductions in resting SBP were consistent with concomitant reductions of 16 mmHg and 5 mmHg in nighttime ambulatory SBP as shown in Figure 3, respectively. Since BP measurements at night are considered to be basal BP and represent the true BP status of an individual (Mahabala et al., 2013), the clinically meaningful reductions in nighttime SBP provide insight into the efficacy of IHG training in medicated hypertensive individuals.

Recent research has found that there are inter-individual differences in the exercise response given a specific exercise amount and intensity (Bouchard & Rankinen,

2001; Hautala et al., 2006; Ross et al., 2015). Moreover, it has been shown that additional exercise intensity and/or frequency is needed in certain individuals in order to achieve the desired response from exercise, with the desired response ranging from increased cardiorespiratory fitness (VO_{2max}) to decreased BP (Bouchard & Rankinen, 2001; Ross et al., 2015). Importantly, greater volumes of exercise are associated with a lower probability of being a non-responder (Sisson et al., 2009). Therefore, IHG training 3 times per week may be frequent enough for some individuals to produce a BP-lowering effect (participants #3 and #4), but may not be enough for others (participants #1 and #2). Consequently, individuals not experiencing a BP-lowering effect from IHG training (non-responders) may just need a slight increase in exercise frequency and/or intensity in order to achieve the BP-lowering effects. The type of medication and/or the combination of antihypertensive medications could also have an effect on IHG-responsiveness. Participants #3 and #4 had the greatest response to IHG training, both were on different medications, with participant #3 being on an ACE inhibitor and β-blocker, while participant #4 was taking a diuretic. Although the BP-lowering mechanism has not been fully elucidated, diuretics have been shown to decrease total peripheral resistance (TPR) (Duarte & Cooper, 2010). In addition, ACE inhibitors, which prevent the formation of the vasoconstrictor angiotensin, also decrease TPR (Sweitzer, 2003). It is possible that these medication-induced reductions in TPR may have an interaction with the endothelial effects of IHG training. The increased vasodilation from diuretics and ACE inhibitors may be causing an increased vasodilation following IHG training, which leads to greater reductions in BP as seen in participants #3 and #4.

Participants #1 and #2 had a minimal response to IHG training, and both were

taking a calcium channel blocker (Participant #1 was taking this alone, while Participant #2 was taking this in addition to an ACE inhibitor). Although this subset of individuals is extremely small, it can be speculated that the type of medication could have an effect on IHG-training responsiveness. Calcium channel blockers also reduce TPR by binding to L-type calcium channels on vascular smooth muscle and cardiac tissue to prevent calcium ion influx into the cell membrane (Livada & Shiloah, 2013). It is possible that the reduction of TPR by calcium channel blockers creates a ceiling effect, which prevents IHG training from having long-term endothelial changes in the participants taking this medication.

Although not statistically significant when examined as a cohort, the greatest reductions in BP are observed in those with higher pre-training BP, in accordance with Millar and colleagues (2014). As shown in Figure 1, participants #3 and #4 had the highest baseline resting SBP, and had the greatest reductions in resting SBP. Participants #1 and #2 had lower baseline resting SBP, and did not have any reductions in resting SBP. Taken together, this still demonstrates the effectiveness of IHG training, especially in the poorly controlled hypertensive population who are at greater risk for CVD in comparison to others with lower BP.

A 4-week cessation of training directly following 8 weeks of IHG training resulted in no statistically significant changes in resting SBP, DBP, and MAP, or 24-hour, daytime, and nighttime ambulatory SBP, DBP, and MAP between post-IHG training and post-IHG detraining. In the participants that showed a reduction in BP following the 8 weeks of training (participants #3 and #4), the reductions in resting SBP and MAP, as well as nighttime ambulatory SBP were maintained after the 4 weeks of

detraining. These findings are in accordance with the work by McGowan (2006a) in a similar cohort of medicated hypertensives after 8 weeks of IHG detraining, but these findings must be interpreted with caution because of the small sample size. Other IRT studies examining detraining effects in normotensive participants all reported significant reductions in BP following the exercise intervention, and all BP values returned to baseline following a detraining period of 1-5 weeks (Wiley et al., 1992; Howden et al., 2002; Devereux et al., 2010). It is worth highlighting that these exercise interventions only lasted 4-5 weeks. Millar and colleagues (2014) hypothesized that the rapid nature of the detraining effects from the IRT studies suggests that the BP-reducing mechanisms responsible influence cardiovascular function rather than structure. Therefore, the 8-week exercise intervention in the study by McGowan (2006a) may be enough to influence cardiovascular structure in order to produce and maintain BP reductions for at least 4 weeks post.

Cardiovascular Reactivity as a Predictor of Isometric Handgrip Training Effectiveness

In this study, IHG training effectiveness in lowering resting BP was not shown to be associated with cardiovascular reactivity to the IHG task, which is contrary to hypothesis 3 and is in disagreement with previous studies that have shown the IHG task being associated with IHG training-induced changes in resting BP (Millar et al., 2009; Badrov et al. 2013). The combination of the present study being underpowered and the fact that no significant changes in resting BP were found after 8 weeks of IHG training makes cardiovascular reactivity as a predictor of IHG effectiveness difficult to determine.

A possible reason for the discrepancy is the impact of anti-hypertensive medication. For example, β-blockers prevent catecholamines from binding to their receptor, causing the heart to pump with less intensity, thus reducing HR and BP (Frishman, 2003). Therefore, the medication could be the cause for the lack of SBP reactivity to the IHG task (12 mmHg in comparison to the mean SBP reactivity of 19 mmHg) observed in the individual on a β-blocker (participant #3). In addition, all participants were on a different combination of anti-hypertensive medication, which all to varying extents reduce TPR and/or cause the heart to contract with less intensity. Therefore, it is difficult to compare one participant to another because the impact of the medication is different for each individual.

IHG training effectiveness in lowering ambulatory BP was not shown to be associated with cardiovascular reactivity to the IHG task. Of interest, these findings are in line with the recent work of Somani and colleagues (2017) in healthy, young adults. It is possible that the predictive effects were not carried over to ambulatory BP reductions in normotensive and hypertensive individuals because of the inherently high variability of BP over a 24-hour period and the difficulty of standardizing extraneous, unanticipated factors such as traffic or inclement weather (Somani et al., 2017; Kamarck et al., 2002). However, a study with a greater sample size is needed to better understand the effects of cardiovascular reactivity on ambulatory BP.

Participant's Perception of Isometric Handgrip Training

IHG training is not routinely prescribed in clinical practice (McGowan et al., 2017), yet there is a significant amount of evidence to show that many people can benefit

from this treatment (Inder et al., 2016). In order to shift this paradigm, the feasibility of IHG training as a long-term BP-lowering treatment was investigated by having participants complete an exit scan following the completion of the study. The time efficiency of IHG training was supported by all participants in strong agreement with the statement, "I found that training 3 times per week was manageable", as well as all participants in strong disagreement or disagreement with the statement, "I felt it was difficult finding the time to train". Additionally, participants seemed to enjoy IHG training, with all participants either in agreement or strong agreement with the statements, "I enjoyed handgrip training", "If the option were available, I would continue to train", as well as, "I would recommend handgrip training to others". This is important because individuals may be more inclined to continue using an exercise modality that they enjoy in comparison to one that they do not find pleasant. Moreover, all participants were either in agreement or strong agreement with the statements, "I felt better after handgrip training for 8 weeks" and "I believe that my health has improved after handgrip training for 8 weeks". Not only are individuals enjoying IHG training on an acute basis during training, but also believe they feel better and healthier on a more long-term basis because of IHG training. Therefore, it is possible that the simplicity, convenience, and time-efficiency (i.e., 12 minutes per day, 3 times per week) of IHG training may lead to greater adherence in comparison to other traditional forms of anti-hypertensive therapy.

2.6 Limitations

Due to the small sample size and observed power of resting SBP and 24-hour ambulatory SBP being 0.086 and 0.129, respectively, inferences cannot be drawn from the data and all results should be interpreted with caution. Taking attrition into

consideration, a sample size of 30 would have provided sufficient power of 0.8. The low power observed in this study limits the probability that null hypotheses would be correctly rejected. Although various modalities were used to advertise the study throughout the Windsor-Essex community, the substantial time commitment (2-3 times per week for 12 weeks) and the specific inclusion/exclusion criteria are examples of limiting factors influencing participation. It is possible that a better incentive to participant in the research study, for example, a gift card worth more money, may facilitate more participants being interested in the study. Although many BP-influencing factors were controlled during each testing session, such as diet, caffeine and alcohol intake, vigorous exercise, and time of day, that fact that BP was measured at only three time points over a 12-week period may limit the precision of the BP readings.

2.7 **Future Research**

A novel and important finding of this study was that participants tended to view IHG training as positive, which provides evidence that IHG training is an enjoyable and time-effective exercise modality. It is possible that future studies with a greater sample size may benefit from having more frequent BP measurement sessions, such as measuring resting and ambulatory BP each week, in order to obtain a more precise measurement of each participant's BP. There might also be a benefit to extending the length of the study beyond 12 weeks to gain insight into the long-term BP effects associated with IHG training.

2.7 References

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

Brook, R. D., Appel, L. J., Rubenfire, M., Ogedegbe, G., Bisognano, J. D., Elliott, W. J., ... & Townsend, R. R. (2013). Beyond medications and diet: alternative approaches to lowering blood pressure. *Hypertension*, *61*, 1360-1383.

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.

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.

Bouchard, C., & Rankinen, T. (2001). Individual differences in response to regular physical activity. *Medicine and Science in Sports and Exercise*, *33*, S446-S451.

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

Chobanian, A. V., Bakris, G. L., Black, H. R., Cushman, W. C., Green, L. A., Izzo, J. L., ... & Roccella, E. J. (2003). Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension*, *42*, 1206-1252.

Colley, R. C., Garriguet, D., Janssen, I., Craig, C. L., Clarke, J., & Tremblay, M. S. (2011). Physical activity of Canadian adults: accelerometer results from the 2007 to 2009 Canadian Health Measures Survey. *Health Reports*, *22*, 7-14.

da Cunha Nascimento, D., Tibana, R. A., Benik, F. M., Fontana, K. E., Neto, F. R., de Santana, F. S., ... & Balsamo, S. (2014). Sustained effect of resistance training on blood pressure and hand grip strength following a detraining period in elderly hypertensive women: a pilot study. *Clinical Interventions in Aging*, *9*, 219-225.

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.

Ebben, W., & Brudzynski, L. (2008). Motivations and barriers to exercise among college students. *Journal of Exercise Physiology Online*, *11*, 1-11.

Frishman, W. H. (1988). Beta-adrenergic blockers. *The Medical Clinics of North America*, *72*, 37-81.

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.

Go, A. S., Mozaffarian, D., Roger, V. L., Benjamin, E. J., Berry, J. D., Blaha, M. J., ... & Stroke, S. S. (2014). Heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation*, *129*, e28-e292.

Hautala, A. J., Kiviniemi, A. M., Mäkikallio, T. H., Kinnunen, H., Nissilä, S., Huikuri, H. V., & Tulppo, M. P. (2006). Individual differences in the responses to endurance and resistance training. *European Journal of Applied Physiology*, *96*, 535-542.

Hemmelgarn, B. R., Chen, G., Walker, R., McAlister, F. A., Quan, H., Tu, K., ... & Campbell, N. (2008). Trends in antihypertensive drug prescriptions and physician visits in Canada between 1996 and 2006. *Canadian Journal of Cardiology*, *24*, 507-512.

Howden, R., Lightfoot, J. T., Brown, S. J., & Swaine, I. L. (2002). The effects of isometric exercise training on resting blood pressure and orthostatic tolerance in humans. *Experimental Physiology*, *87*, 507-515.

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.

Kamarck, T. W., Janicki, D. L., Shiffman, S., Polk, D. E., Muldoon, M. F., Liebenauer, L. L., & Schwartz, J. E. (2002). Psychosocial demands and ambulatory blood pressure: a field assessment approach. *Physiology & Behavior*, *77*, 699-704.

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.

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. *The Lancet, 360*, 1903-1913.

Livada, R., & Shiloah, J. (2014). Calcium channel blocker-induced gingival enlargement. *Journal of Human Hypertension*, *28*, 10-14.

Mahabala, C., Kamath, P., Bhaskaran, U., Pai, N. D., & Pai, A. U. (2013). Antihypertensive therapy: nocturnal dippers and nondippers. Do we treat them differently? *Vascular Health and Risk Management*, *9*, 125-133.

McGowan, C. L**.** (2006a). Isometric Handgrip Training and Arterial Blood Pressure: Effects and Mechanisms (PhD Thesis). *Hamilton: McMaster University*.

McGowan, C. L., Visocchi, A., Faulkner, M., Verduyn, R., Rakobowchuk, M., Levy, A. S., ... & MacDonald, M. J. (2006b). Isometric handgrip training improves local flow-mediated dilation in medicated hypertensives. *European Journal of Applied Physiology*, *98*, 355-362.

McGowan, C. L., Proctor, D. N., Swaine, I., Brook, R. D., Jackson, E. A., & Levy, P. D. (2017). Isometric handgrip as an adjunct for blood pressure control: a primer for clinicians. *Current Hypertension Reports*, *6*, 1-8.

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

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

Millar, P. J., Levy, A. S., McGowan, C. L., McCartney, N., & MacDonald, M. J. (2013). Isometric handgrip training lowers blood pressure and increases heart rate complexity in medicated hypertensive patients. *Scandinavian Journal of Medicine & Science in Sports*, *23*, 620-626.

Millar, P. J, 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.

O'Brien, E., Beevers, G., & Lip, G. Y. (2001). Blood pressure measurement: Part III-Automated sphygmomanometry: ambulatory blood pressure measurement. *British Medical Journal*, *322*, 1110-1114.

Ogedegbe, G., & Pickering, T. (2010). Principles and techniques of blood pressure measurement. *Cardiology Clinics*, *28*, 571-586.

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

Ross, R., de Lannoy, L., & Stotz, P. J. (2015). Separate effects of intensity and amount of exercise on interindividual cardiorespiratory fitness response. *Mayo Clinic Proceedings, 90*, 1506-1514.

Sisson, S. B., Katzmarzyk, P. T., Earnest, C. P., Bouchard, C., Blair, S. N., & Church, T. S. (2009). Volume of exercise and fitness non-response in sedentary, post-menopausal women. *Medicine and Science in Sports and Exercise*, *41*, 539-545.

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.* Paper 5285.

Somani, Y., 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.

Staessen, J., Fagard, R., Lijnen, P., Thijs, L., Van Hoof, R., & Amery, A. (1991). Ambulatory blood pressure monitoring in clinical trials. *Journal of Hypertension. Supplement: Official Journal of the International Society of Hypertension*, *9*, S13-S19.

Statistics Canada. (2015a). The 10 Leading Causes of Death, 2012. Retrieved from: http://www.statcan.gc.ca/pub/82-625-x/2015001/article/14296-eng.htm

Statistics Canada. (2015b). Directly measured physical activity of adults, 2012 and 2013. Retrieved from: http://www.statcan.gc.ca/pub/82-625-x/2015001/article/14135-eng.htm

Stiller-Moldovan, C., Kenno, K., & McGowan, C.L. (2012). 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.

Wiley, R., Dunn, C., Cox, R., Hueppchen, A., & Scott, M. (1992). Isometric exercise training lowers resting blood pressure. *Medicine & Science in Sports & Exercise*, *24*, 749-54.

Wilkins K., Campbell, N. R., Joffres, M. R., McAlister, F. A., Nichol, M., Quach, S., Johansen, H. L., & Tremblay, M. S. (2010). Blood pressure in Canadian adults. *Statistics Canada Health Reports, 21,* 37-46.

Windsor-Essex County Health Unit. (2017). High Blood Pressure in Windsor-Essex County. Retrieved from: https://www.wechu.org/reports/high-blood-pressure-windsor-essex-county

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

World Health Organization (2017). Cardiovascular Diseases. Retrieved from: http://www.who.int/mediacentre/factsheets/fs317/en/

Appendices

Appendix A — Recruitment Materials

Investigators at the University of Windsor are currently looking for individuals on medication for high blood pressure to participate in a study examining the effects of isometric handgrip exercise on blood pressure. If you are interested and would like more information please contact Michael Pearl, BSc: (519)-253-3000 ext. 4979 or pearlm@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 on medication for high 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 twelve weeks of isometric handgrip exercise training on your blood pressure. For more information please contact Michael Pearl at 519-253-3000 ex. 4979 or pearlm@uwindsor.ca."

Appendix B — Ethics Approval of Study

University of Windsor

Office of the Research Ethics Board
401 Sunset Avenue
Windsor, Ontario, Canada N9B 3P4
T 519-253-3000 ext. 3948
www.uwindsor.ca/reb

Today's Date: June 19, 2014
Principal Investigator: Dr. Cheri McGowan/Dr. Kevin Milne
REB Number: 31664
Research Project Title: REB# 14-110: Application of isometric resistance exercise to treat hypertension
Clearance Date: June 19, 2014
Project End Date: August 31, 2017
Milestones:
Renewal Due-2017/08/31(Pending)
Renewal Due-2016/07/01(Pending)
Renewal Due-2015/07/01(Pending)

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

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

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

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

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

We wish you every success in your research.

Pierre Boulos, Ph.D.
Chair, Research Ethics Board
Lambton Tower, Room 1102 A
University of Windsor
519-253-3000 ext. 3948
Email: ethics@uwindsor.ca

Appendix C — Consent to Participate in Research

Title of Study: Isometric Resistance Exercise to Treat Hypertension

You are asked to participate in a 12-week isometric exercise training research study conducted at the University of Windsor. Your total time commitment for the entire study is ~ 24 hours: a) determining if you qualify to participate in the study (~1 hour), b) testing days (~5 hours total), and c) exercise training (~30 minutes, 3X per week; ~18 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). For questions or concerns during non-working hours, please contact Cheri McGowan, PhD via cell phone at XXX-XXX-XXXX.

PURPOSE OF THE STUDY

In Canada, 1 in 5 people have high blood pressure or resting blood pressure numbers that are ≥ 140/90 mmHg, and it is the number one reason why Canadians see their doctor. Many people taking medicine for high blood pressure do not have their pressure as low as it should be and this is a big problem.

Our research group has shown that isometric (constant squeeze) exercise training using a handgrip lowers resting blood pressure in people who have high blood pressure, and even in those with normal blood pressure. Squeezing a handgrip for 2 minutes, 4 times, 3 times a week for 8 to 10 weeks has been suggested by the American Heart Association as a potentially promising new way to lower BP, and also seems to work even in people taking blood pressure medication.

Doctors often do not suggest handgrip treatment. This may be because Canadian doctors, researchers, and people like yourself living with high blood pressure do not know if handgrip treatment also lowers blood pressure during everyday life, if blood pressure stays low once the exercise program stops, or for other reasons of which we are unaware. Our study will help answer these questions.

In order to participate in this study you must currently be on medication for blood pressure and have a resting blood pressure greater than or equal to 120/80 mmHg. Your primary health care provider (e.g., family doctor, nurse practitioner) must also agree that it is okay for you to participate. If you have been in the hospital in the last 3 months, have changed your medication in the past 2 months, plan on being away for longer than 1 week during the study period, or 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 using an automatic device by placing a cuff around 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. If your resting blood pressure is ≥ 120/80 mmHg, but < 159/99 mmHg your next visit will be scheduled.

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 ≥ 120/80 mmHg, you will then practice all parts of the study including 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-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 date to complete the Testing Day. All testing days will be separated by at least 24 hours.

Testing Days (approximately 60 minutes in-lab; 24-hours offsite):
You will be asked not to exercise vigorously (e.g., exercise that causes you to breathe 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, 4 hours after eating. On testing days, you will be asked to go to the washroom before testing, as a full bladder can increase your blood pressure.

Upon entering the lab, you will first sit at a table and answer 6 to 17 questions on paper. You will complete this by yourself, but we will be nearby to answer any questions you may have. Next, your resting blood pressure will be measured in the same way that it was measured in the previous visits. You will squeeze a handgrip at 30% of your hardest squeeze for 2-minutes while your blood pressure is measured. At the end of the testing section, we will send you home with a machine that will record your blood pressure for the

next 24 hours. The morning following, you will return the device to us. On the final testing day, you will be asked to complete an additional exit scan consisting of 11 questions about your handgrip training experience.

Training Days (approximately 30 minutes)
You will be asked to perform 3 handgrip exercises sessions per week, identical to the one you performed on Visit 2 (4, 2 minute squeezes, switching hands with each squeeze, with a minute of rest between) for 8 weeks. Again, squeezes will be performed at 30% of your hardest squeeze. 2 out of the 3 sessions will be performed in the PACR lab, while 1 can be done at home. All of your sessions in the lab 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 also monitor any changes in diet, exercise or medication at each visit on a log sheet, and ask that you sign the log at each visit to show that you still would like to be involved with the study. We will also have a form to keep track of how many times you go to see your health care provider about your high blood pressure. At the end of 8 weeks, you will have your resting and ambulatory blood pressure measured during another Testing Day, as described above.

Following 8 weeks of training, you will be randomly (by chance) selected to be in 1 of 2 groups Depending on your group, you may or may not perform the handgrip for another 4 weeks. If you are in Group 1, you will continue to train 3 times per week for an additional 4 weeks. If you are in Group 2, you will not train at all for the additional 4 weeks. At the end of this 4-week period, both groups will have a final Testing Day to measure blood pressure again.

	Testing Hours	Initial Training Phase Hours	Post-Training Phase Hours	**TOTAL**
Group 1	6	12	6	**24 hours**
Group 2	6	12	4	**22 hours**

At the end of each IHG training session, the IHG displays a compliance score out of 100. A score >90 needs to be achieved in order for the training session to count. 8 weeks of IHG training consists of 24 training sessions (3 times per week). You will need to complete at least 80% or 20 training sessions during the 8 weeks in order to remain eligible in the study. During the additional 4 weeks of training (12 training sessions) if you are in Group 1, you will need to complete at least 80% or 10 training sessions during the 4 weeks in order to remain eligible in the study. If you miss a training session during the training period, you will be encouraged to make up for the missed training session during the next week of training. Each IHG training session should be separated by at least 12 hours. If you miss four or more training sessions without making up for any training sessions, or if you go seven consecutive days without training, you may continue participating in the study, but your data will not be used for full analysis. If you are out of town for an extended period of time, you will be encouraged to bring an IHG device with you and continue your normal training routine. If you plan on being away during the study period for longer than 1 week, it is encouraged that we wait until you are back before we start the training protocol.

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. 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. If handgrip training lowers blood pressure in the people in our study, other patients may use it if their blood pressure is higher than it should be despite taking blood pressure medicine. Our work may encourage doctors to suggest this exercise to their patients.

COMPENSATION FOR PARTICIPATION

You will be reimbursed for parking during the study, as well as for money paid to have your health care provider form completed. You will receive a $20.00 Gift Certificate for Canadian Tire and 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 informed consent and health care provider documents. 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. If you choose to withdraw, in most cases we will ask to use the data collected up to the time of your withdrawal, but

you can request that any and all of your data be destroyed, again without consequence. The investigator may withdraw you from this research if circumstances arise which warrant doing so (e.g., change in medication, nutrition or physical activity status). All parking expenses and health care provider document expenses incurred to date will be reimbursed.

FEEDBACK OF THE RESULTS OF THIS STUDY TO THE PARTICIPANTS

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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 "Application of isometric resistance exercise to treat hypertension" as described herein. My questions have been answered to my satisfaction, and I agree to participate in this study. I have been given a copy of this form.

_____

Name of Participant

_____ _____

Signature of Participant Date

SIGNATURE OF INVESTIGATOR

These are the terms under which I will conduct research.

_____ _____

Signature of Investigator Date

Appendix D — Letter of Information

Title of Study: Isometric Resistance Exercise to Treat Hypertension

You are asked to participate in a 12-week isometric exercise training research study conducted at the University of Windsor. Your total time commitment for the entire study is ~ 24 hours: a) determining if you qualify to participate in the study (~1 hour), b) testing days (~5 hours total), and c) exercise training (~30 minutes, 3X per week; ~18 hours total).

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You will be reimbursed for parking during the study, as well as for money paid to have your health care provider form completed. You will receive a $20.00 Gift Certificate for Canadian Tire and 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 informed consent and health care provider documents. 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. If you choose to withdraw, in most cases we will ask to use the data collected up to the time of your withdrawal, but

you can request that any and all of your data be destroyed, again without consequence. The investigator may withdraw you from this research if circumstances arise which warrant doing so (e.g., change in medication, nutrition or physical activity status). All parking expenses and health care provider document expenses incurred to date will be reimbursed.

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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 INVESTIGATOR

These are the terms under which I will conduct research.

_____ _____

Signature of Investigator Date

Appendix E — 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 Check Yes or No: Yes No

1. Have you ever been hospitalized?.....o o
   If yes, please specify?
   _____
   Have you ever had surgery? .....o o
   If yes, please specify?
   _____
2. Are you presently taking any medications or pills (including aspirin and other over-the-counter medication)?.....o o
   If yes, please specify?
   _____
   Are you presently taking any vitamins, supplements, and/or herbal supplements? .....o o
3. Do you have any allergies (medicine, food, bees or other stinging insects)?.....o o
   If yes, please specify?
   _____
4. Have you ever passed out during or after exercise?.....o o
   Have you ever been dizzy during or after exercise? .....o o
   Have you ever had chest pain during or after exercise? .....o o
   Do you have high blood pressure (hypertension) or low blood pressure (hypotension)? .....o o
   Have you ever been told that you have a kidney problem? .....o o
   Have you ever been told that you have joint instability? .....o o
   Have you ever been told that you have a stomach problem? .....o o
   Have you ever been told that you have a heart problem? .....o o
   Have you ever been told that you have a heart murmur? .....o o
   Do you have a machine that regulated your heart beat? .....o o
   Have you ever had racing of your heart or skipped heartbeats? .....o o
   Has anyone in your family died of heart problems or a sudden death before age 50? .....o o
5. Do you have any skin problems (itching, rashes, acne)? .....o o
   If you get a cut, does it take you a long time to stop bleeding? .....o o
   If you experience a blow to a muscle, do you bruise easily? .....o o
6. Do you have Diabetes? o o
7. Do you have Asthma or any other breathing problems? .....o o
   If yes, please specify?
   _____
8. Do you have any type of cardiovascular disease? .....o o
   If yes, please specify? _____
9. Have you had any other medical problems (infectious mononucleosis, etc.)? .....o o
10. Have you had any medical problems since your last physical? .....o o
11. Do you smoke? .....o o
12. Do you aerobically exercise (e.g., walking) for $\geq$ 30 minutes, > 2 times per week? .....o o

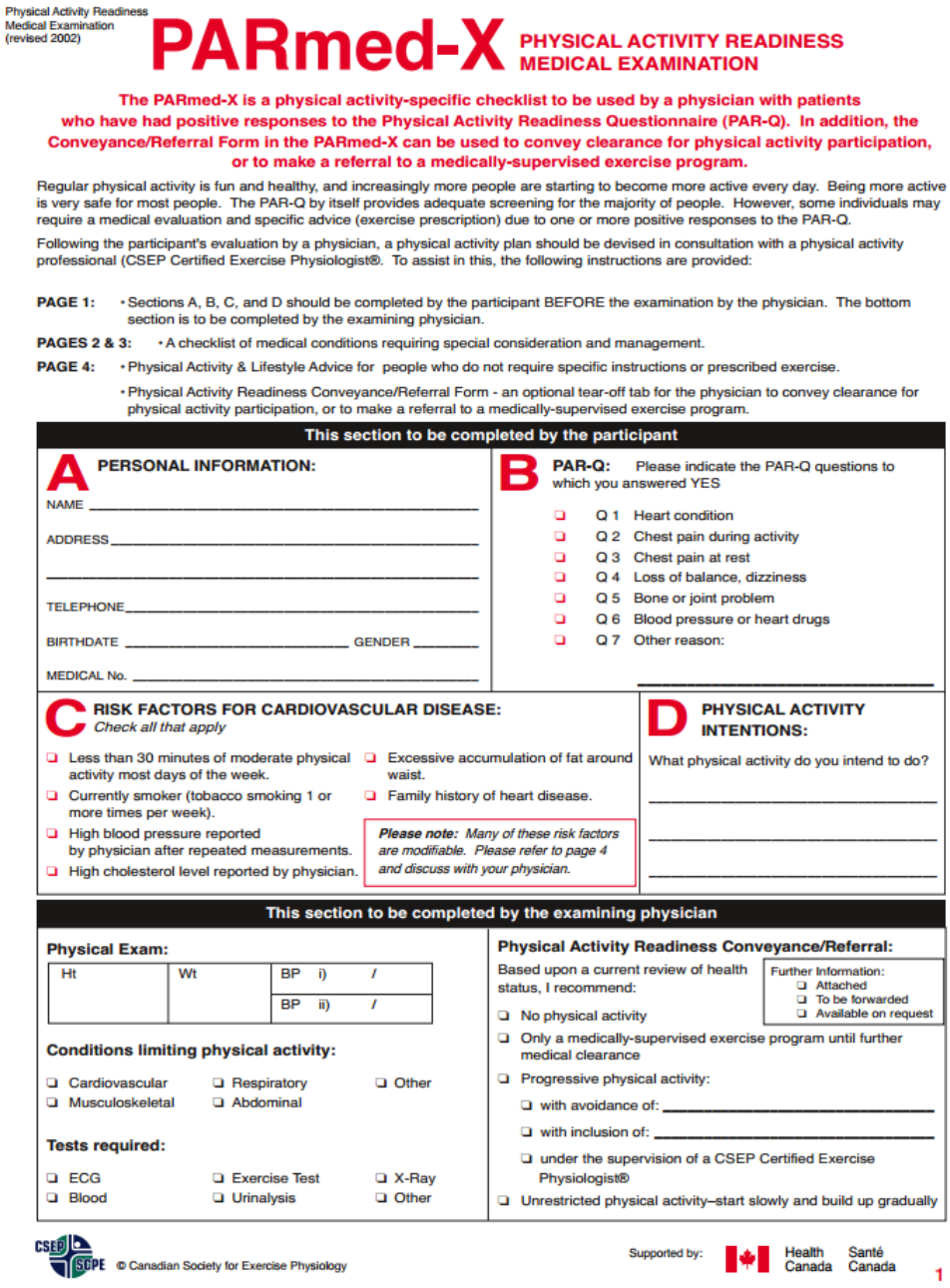
Please explain any physical limitations that may prevent you from completing this study:

_____

Appendix F — Resting Blood Pressure and Heart Rate Device

Dinamap Carescape v100, Critikon, Tampa, Florida, USA

Appendix G — Physical Activity Readiness Medical Examination



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

Tests required:

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

CSEP SCPE © Canadian Society for Exercise Physiology

Supported by: Health Canada Santé Canada

1

Required: Patient's Hypertensive Status (Choose one ☑): 1) Primary Hypertension ☐
2) Secondary Hypertension ☐

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...

	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...

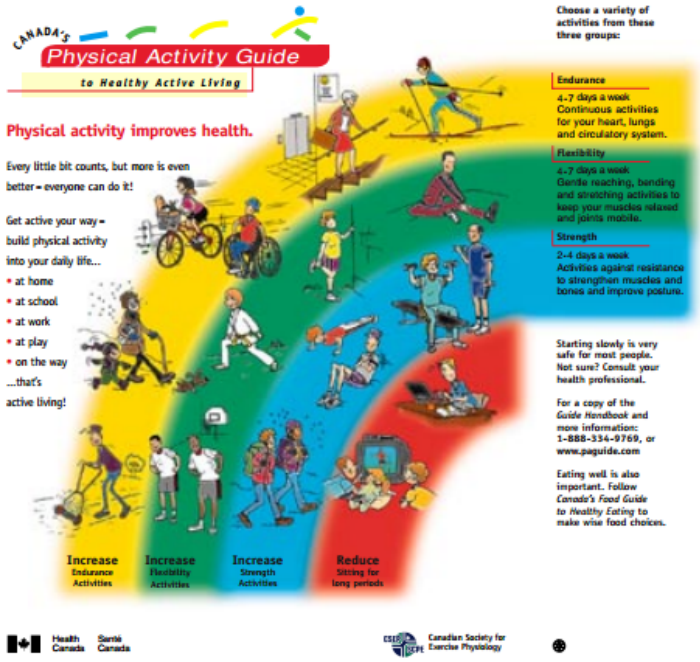
It is a prudent practice to retain the completed Physical Activity Readiness Conveyance/Referral Form in the participant's file.

Supported by: Health Canada Santé Canada

Continued on page 4...

Physical Activity Readiness
Medical Examination
(revised 2002)

PARmed-X PHYSICAL ACTIVITY READINESS MEDICAL EXAMINATION



Choose a variety of activities from these three groups:

Endurance
4–7 days a week
Continuous activities for your heart, lungs and circulatory system.

Flexibility
4–7 days a week
Gentle reaching, bending and stretching activities to keep your muscles relaxed and joints mobile.

Strength
2–4 days a week
Activities against resistance to strengthen muscles and bones and improve posture.

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

For a copy of the *Guide Handbook* and more information: 1-888-334-9769, or www.paguide.com

Eating well is also important. Follow *Canada's Food Guide to Healthy Eating* to make wise food choices.

Get Active Your Way, Every Day – For Life!

Scientists say accumulate 60 minutes of physical activity every day to stay healthy or improve your health. As you progress to moderate activities you can cut down to 30 minutes, 4 days a week. Add-up your activities in periods of at least 10 minutes each. Start slowly... and build up.

Time needed depends on effort

Very Light Effort	Light Effort 60 min/week	Moderate Effort 30–60 min/week	Vigorous Effort 20–30 min/week	Maximum Effort
• Strolling • Dusting	• Light walking • Volleyball • Easy gardening • Stretching	• Brisk walking • Biking • Raking leaves • Swimming • Dancing • Water aerobics	• Aerobics • Jogging • Hockey • Basketball • Fast swimming • Fast dancing	• Sprinting • Racing

Range needed to stay healthy

You Can Do It – Getting started is easier than you think

Physical activity doesn t have to be very hard. Build physical activities into your daily routine.

- Walk whenever you can – get off the bus early, use the stairs instead of the elevator.
- Reduce inactivity for long periods, like watching TV.
- Get up from the couch and stretch and bend for a few minutes every hour.
- Play actively with your kids.
- Choose to walk, wheel or cycle for short trips.
- Start with a 10 minute walk – gradually increase the time.
- Find out about walking and cycling paths nearby and use them.
- Observe a physical activity class to see if you want to try it.
- Try one class to start – you don t have to make a long-term commitment.
- Do the activities you are doing now, more often.

Benefits of regular activity:	Health risks of inactivity:
• better health • improved fitness • better posture and balance • better self-esteem • weight control • stronger muscles and bones • feeling more energetic • relaxation and reduced stress • continued independent living in later life	• premature death • heart disease • obesity • high blood pressure • adult-onset diabetes • osteoporosis • stroke • depression • colon cancer

Health Canada / Santé Canada

Canadian Society for Exercise Physiology

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 Documents

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: Application of Isometric Resistance Training to Treat Hypertension (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.

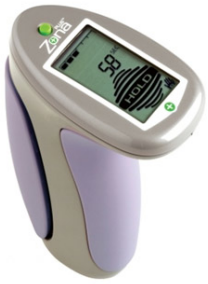
Sincerely,
Dr. Cheri McGowan, PhD
Dr. Kevin Milne, PhD
Assistant Professors
Department of Kinesiology
Faculty of Human Kinetics
University of Windsor

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: Application of Isometric Resistance Training to Treat Hypertension. I have approved my patient's participation in your study.

Appendix I — Isometric Handgrip



ZonaPLUS, Zona HEALTH, Boise, Idaho, USA

Appendix J — Exit Scan

Using the scale from 1 – 5 (see below), please answer questions #1-9 by circling a number from 1 to 5.

1 = Strongly Disagree

2 = Disagree

3 = Undecided

4 = Agree

5 = Strongly Agree

1) I enjoyed handgrip training.

1 2 3 4 5

2) I found handgrip training challenging.

1 2 3 4 5

3) I found that training 3 times per week was manageable.

1 2 3 4 5

4) I felt it was difficult finding the time to train using the handgrip.

1 2 3 4 5

5) If the option was available, I would continue to train using the handgrip.

1 2 3 4 5

6) I would be willing to pay for the current cost of a handgrip (approximately $600.00).

1 2 3 4 5

7) I felt better after handgrip training for 8 weeks.

1 2 3 4 5

8) I believe that my health has improved after handgrip training for 8 weeks.

1 2 3 4 5

9) I would recommend handgrip training to others.

1 2 3 4 5

10) My ideal handgrip training frequency per week would be: Check one ☑

☐ 0 times per week

☐ 1 time per week

☐ 3 times per week

☐ 5 times per week

☐ 7 times per week

11) Do you have anything you would like to add about handgrip training?

_____

_____

_____

Appendix K — 24-hour Ambulatory Blood Pressure Device

SpaceLabs Inc., Redmond, Washington, USA

Appendix L - 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 M — Participant Log

Name:_____

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 N – Additional Participant Log

Additional Exercise Log

Please document any additional exercise you participate in during the week of _____ to _____
Include information on dates, type of exercise (i.e. walking, weight training exercise,
exercise, yoga, etc.), intensity (using the BORG RPE Scale described on reverse) and the duration
(number of hours) spent on each activity recorded for each date.

Exercise			
Date	**Type of Exercise**	**Intensity**	**Duration**

Modified BORG Rating of Perceived Exertion Scale

For each additional bout of exercise recorded in the chart on the reverse of this sheet, fill in the "Intensity" column with a number corresponding to how challenging you felt the exercise to be.

Rating	Descriptor
0	Nothing at all
0.5	Extremely easy
1	Very easy
2	Easy
3	Moderate
4	Somewhat difficult
5	Difficult
6	
7	Very difficult
8	
9	
10	Maximally difficult

This sheet can be printed on the back of the Additional Exercise Log

Health Care Provider Visits

Please document any visits to your doctor, the emergency room and all hospitalizations related to your high blood pressure during the week of _____ to _____.

Date	**Family Physician or other Health Care Provider**	**Cardiologist or other medical specialist**	**Emergency Room Visits**	**Reason for Visit**

Hospitalizations				
Date Admitted	**Date Released**	**Reason for Hospitalization**	**Symptoms During Stay**	**Treatment Given (e.g., new medication, surgery)**

Medication Changes Log

Please answer the following questions regarding changes to your medication during the month of _____ (weeks _____ to _____). In the case of a "Yes" answer, please describe the change (include the dosage of new medications) in the space provided, or for multiple changes use additional space on the reverse of this sheet.

Has your doctor or nurse practitioner prescribed any **new** medications **in addition** to those you are already taking?

Y N _____

Has your doctor or nurse practitioner **removed** any **existing** prescribed medications?

Y N _____

Has your doctor prescribed a **change in dosage** of any of your **existing** medications?

Y N _____

"I understand that I am able to withdraw from this study (Isometric Resistance Exercise to Treat Hypertension) at any time. Please accept my initials below as an indication of my ongoing consent to participate."

Date	Participant initials

AT HOME JOURNAL:

Participant Code:_____

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 O – Statistical Analysis for Chapter 2

Effects of IHG Training on Resting Blood Pressure and Heart Rate
Resting value Pre-IHG to Post-IHG Training – Dependent t-test

1. Resting SBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre-IHG	134.1667	4	14.47987	7.23994
	Post-IHG	128.2500	4	6.62417	3.31208

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre-IHG - Post-IHG	5.91667	10.77849	5.38925	-11.23432	23.06765	1.098	3	.352

2. Resting DBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre-IHG	76.9167	4	10.14479	5.07239
	Post-IHG	77.8333	4	4.81124	2.40562

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre-IHG - Post-IHG	-.91667	6.20858	3.10429	-10.79591	8.96257	-.295	3	.787

3. Resting MAP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre-IHG	96.0000	4	10.71325	5.35662
	Post-IHG	94.6389	4	4.81199	2.40599

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Pre-IHG - Post-IHG	1.36111	7.22729	3.61364	-10.13912	12.86134	.377	3	.731

4. Resting HR:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre-IHG	60.3333	4	4.57853	2.28927
	Post-IHG	59.9167	4	3.37062	1.68531

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Pre-IHG - Post-IHG	.41667	2.89796	1.44898	-4.19463	5.02796	.288	3	.792

Ambulatory value Pre- to Post-IHG Training – Dependent t-test

1a. 24-hour SBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre-IHG	134.7294	4	14.29104	7.14552
	Post-IHG	132.9256	4	8.73204	4.36602

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre-IHG - Post-IHG	1.80375	7.88512	3.94256	-10.74324	14.35074	.458	3	.678

1b. 24-hour DBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre-IHG	83.3375	4	8.55798	4.27899
	Post-IHG	82.5623	4	5.00771	2.50385

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre-IHG - Post-IHG	.77521	6.18686	3.09343	-9.06946	10.61988	.251	3	.818

1c. 24-hour MAP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre-IHG	100.9559	4	8.43830	4.21915
	Post-IHG	99.5465	4	6.01732	3.00866

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre-IHG - Post-IHG	1.40934	4.81155	2.40577	-6.24690	9.06559	.586	3	.599

1d. 24-hour HR:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre-IHG	63.9660	4	4.42377	2.21188
	Post-IHG	62.6525	4	4.57805	2.28903

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre-IHG - Post-IHG	1.31341	1.08310	.54155	-.41005	3.03687	2.425	3	.094

2a. Daytime SBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre-IHG	137.9430	4	13.00381	6.50190
	Post-IHG	136.7440	4	8.27054	4.13527

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre-IHG - Post-IHG	1.19900	8.64398	4.32199	-12.55551	14.95351	.277	3	.799

2b. Daytime DBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre-IHG	87.0031	4	6.77739	3.38870
	Post-IHG	85.7846	4	4.98145	2.49072

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre-IHG - Post-IHG	1.21853	5.67946	2.83973	-7.81877	10.25582	.429	3	.697

2c. Daytime MAP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre-IHG	104.5376	4	6.39980	3.19990
	Post-IHG	102.8130	4	5.75309	2.87655

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre-IHG - Post-IHG	1.72454	4.78231	2.39116	-5.88519	9.33426	.721	3	.523

2d. Daytime HR:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre-IHG	65.3413	4	4.77629	2.38814
	Post-IHG	63.4924	4	4.44057	2.22028

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre-IHG - Post-IHG	1.84898	1.67330	.83665	-.81362	4.51158	2.210	3	.114

3a. Nighttime SBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre-IHG	124.8507	4	17.94181	8.97091
	Post-IHG	119.6250	4	11.59966	5.79983

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre-IHG - Post-IHG	5.22569	8.38471	4.19235	-8.11624	18.56763	1.246	3	.301

3b. Nighttime DBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre-IHG	72.2986	4	12.51229	6.25614
	Post-IHG	71.3125	4	6.60689	3.30345

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre-IHG - Post-IHG	.98611	5.99276	2.99638	-8.54971	10.52193	.329	3	.764

3c. Nighttime MAP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre-IHG	90.4167	4	14.13792	7.06896
	Post-IHG	88.1563	4	8.42700	4.21350

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre-IHG - Post-IHG	2.26042	6.10663	3.05332	-7.45660	11.97743	.740	3	.513

3d. Nighttime HR:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre-IHG	59.7292	4	4.87785	2.43892
	Post-IHG	59.7188	4	5.17946	2.58973

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre-IHG - Post-IHG	.01042	2.65042	1.32521	-4.20700	4.22783	.008	3	.994

4a. Dipping SBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre-IHG	9.7608	4	4.72622	2.36311
	Post-IHG	12.5600	4	5.68895	2.84447

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre-IHG - Post-IHG	-2.79916	6.74834	3.37417	-13.53728	7.93895	-.830	3	.468

4b. Dipping DBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre-IHG	17.3333	4	7.65393	3.82697
	Post-IHG	16.8379	4	6.26412	3.13206

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre-IHG - Post-IHG	.49539	3.54290	1.77145	-5.14217	6.13294	.280	3	.798

4c. Dipping MAP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre-IHG	13.8611	4	7.89901	3.94951
	Post-IHG	14.2668	4	6.20863	3.10432

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre-IHG - Post-IHG	-.40569	5.74363	2.87181	-9.54508	8.73370	-.141	3	.897

Cardiovascular Reactivity as a Predictor of IHG Training Effectiveness
Correlation Analysis

1. Resting SBP

	ΔSBP (mmHg)	***r***	***P***	**ΔDBP (mmHg)**	***r***	***P***	**ΔHR (bpm)**	***r***	***P***
IHGT	19 ± 9	0.584	0.416	11 ± 6	0.705	0.295	5 ± 3	0.456	0.544

2a. 24-hour SBP

	IHGT-SBP	IHGT-DBP	IHGT-HR
r	0.510	0.968	0.846
P	0.659	0.162	0.358

IHGT, isometric handgrip task; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate

2b. Daytime SBP

	IHGT-SBP	IHGT-DBP	IHGT-HR
r	-0.571	-0.983	-0.882
P	0.613	0.117	0.313

IHGT, isometric handgrip task; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate

2c. Nighttime SBP

	IHGT-SBP	IHGT-DBP	IHGT-HR
r	0.479	0.958	0.826
P	0.682	0.185	0.381

IHGT, isometric handgrip task; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate

Effect of IHG Training on Maximum Voluntary Contraction

Repeated Measures ANOVA

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.
factor1	Sphericity Assumed	646.560	23	28.111	1.518	.094
	Greenhouse-Geisser	646.560	2.490	259.648	1.518	.284
	Huynh-Feldt	646.560	15.613	41.412	1.518	.135
	Lower-bound	646.560	1.000	646.560	1.518	.306
Error(factor1)	Sphericity Assumed	1277.617	69	18.516		
	Greenhouse-Geisser	1277.617	7.470	171.024		
	Huynh-Feldt	1277.617	46.839	27.277		
	Lower-bound	1277.617	3.000	425.872		

Effects of IHG Detraining on Resting Blood Pressure and Heart Rate

Resting value Post-IHG Training to Detraining – Dependent t-test

1. Resting SBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Post_IHG	128.2500	4	6.62417	3.31208
	Detraining	123.2500	4	14.92793	7.46397

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Post_IHG - Detraining	5.00002	13.52911	6.76456	-16.52781	26.52786	.739	3	.513

2. Resting DBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Post_IHG	77.8333	4	4.81124	2.40562
	Detraining	70.1667	4	4.63880	2.31940

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Post_IHG - Detraining	7.66668	7.31815	3.65908	-3.97814	19.31149	2.095	3	.127

3. Resting MAP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Post_IHG	94.6389	4	4.81199	2.40599
	Detraining	87.8611	4	7.91487	3.95743

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Post_IHG - Detraining	6.77779	9.33112	4.66556	-8.07010	21.62568	1.453	3	.242

4. Resting HR:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Post_IHG	59.9167	4	3.37062	1.68531
	Detraining	58.7500	4	2.28321	1.14160

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Post_IHG - Detraining	1.16668	4.49280	2.24640	-5.98238	8.31573	.519	3	.639

Resting value Pre-IHG Training to Detraining – Dependent t-test

1. Resting SBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre_IHG	134.1667	4	14.47987	7.23994
	Detraining	123.2500	4	14.92793	7.46397

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre_IHG - Detraining	10.91669	14.98487	7.49243	-12.92757	34.76096	1.457	3	.241

2. Resting DBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre_IHG	76.9167	4	10.14479	5.07239
	Detraining	70.1667	4	4.63880	2.31940

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre_IHG - Detraining	6.75000	10.96248	5.48124	-10.69374	24.19375	1.231	3	.306

3. Resting MAP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre_IHG	96.0000	4	10.71325	5.35662
	Detraining	87.8611	4	7.91487	3.95743

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre_IHG - Detraining	8.13890	12.23345	6.11673	-11.32725	27.60505	1.331	3	.275

4. Resting HR:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre_IHG	60.3333	4	4.57853	2.28927
	Detraining	58.7500	4	2.28321	1.14160

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre_IHG - Detraining	1.58334	6.42551	3.21276	-8.64108	11.80777	.493	3	.656

Ambulatory value Post-IHG Training to Detraining – Dependent t-test

1a. 24-hour SBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Post_IHG	132.9256	4	8.73204	4.36602
	Detraining	127.7488	4	8.98379	4.49189

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Post_IHG - Detraining	5.17689	5.17536	2.58768	-3.05825	13.41204	2.001	3	.139

1b. 24-hour DBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Post_IHG	82.5623	4	5.00771	2.50385
	Detraining	78.0137	4	3.65028	1.82514

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Post_IHG - Detraining	4.54865	3.64470	1.82235	-1.25087	10.34818	2.496	3	.088

1c. 24-hour MAP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Post_IHG	99.5465	4	6.01732	3.00866
	Detraining	95.0728	4	5.77430	2.88715

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Post_IHG - Detraining	4.47374	3.03322	1.51661	-.35280	9.30027	2.950	3	.060

1d. 24-hour HR:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Post_IHG	62.6525	4	4.57805	2.28903
	Detraining	60.8874	4	5.14356	2.57178

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Post_IHG - Detraining	1.76516	5.60328	2.80164	-7.15090	10.68123	.630	3	.573

2a. Daytime SBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Post_IHG	136.7440	4	8.27054	4.13527
	Detraining	131.9696	4	9.79517	4.89758

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Post_IHG - Detraining	4.77433	6.99634	3.49817	-6.35840	15.90707	1.365	3	.266

2b. Daytime DBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Post_IHG	85.7846	4	4.98145	2.49072
	Detraining	81.8860	4	4.55315	2.27658

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Post_IHG - Detraining	3.89856	5.02234	2.51117	-4.09310	11.89022	1.552	3	.218

2c. Daytime MAP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Post_IHG	102.8130	4	5.75309	2.87655
	Detraining	98.7285	4	6.82522	3.41261

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Post_IHG - Detraining	4.08452	4.54636	2.27318	-3.14975	11.31879	1.797	3	.170

2d. Daytime HR:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Post_IHG	63.4924	4	4.44057	2.22028
	Detraining	62.4196	4	6.13395	3.06697

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Post_IHG - Detraining	1.07273	6.81209	3.40605	-9.76683	11.91229	.315	3	.773

3a. Nighttime SBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Post_IHG	119.6250	4	11.59966	5.79983
	Detraining	115.1563	4	9.97046	4.98523

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Post_IHG - Detraining	4.46875	4.26636	2.13318	-2.31998	11.25748	2.095	3	.127

3b. Nighttime DBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Post_IHG	71.3125	4	6.60689	3.30345
	Detraining	66.7500	4	3.65006	1.82503

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Post_IHG - Detraining	4.56250	4.90376	2.45188	-3.24048	12.36548	1.861	3	.160

3c. Nighttime MAP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Post_IHG	88.1563	4	8.42700	4.21350
	Detraining	84.2902	4	5.17727	2.58863

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Post_IHG - Detraining	3.86607	4.27709	2.13854	-2.93973	10.67187	1.808	3	.168

3d. Nighttime HR:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Post_IHG	59.7188	4	5.17946	2.58973
	Detraining	56.8929	4	3.48014	1.74007

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Post_IHG - Detraining	2.82589	3.82747	1.91374	-3.26447	8.91625	1.477	3	.236

4a. Dipping SBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Post_IHG	12.5600	4	5.68895	2.84447
	Detraining	12.7503	4	3.42110	1.71055

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Post_IHG - Detraining	-.19031	4.33369	2.16684	-7.08617	6.70555	-.088	3	.936

4b. Dipping DBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Post_IHG	16.8379	4	6.26412	3.13206
	Detraining	18.4735	4	1.45434	.72717

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Post_IHG - Detraining	-1.63554	6.83985	3.41992	-12.51926	9.24818	-.478	3	.665

4c. Dipping MAP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Post_IHG	14.2668	4	6.20863	3.10432
	Detraining	14.5599	4	2.74886	1.37443

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Post_IHG - Detraining	-.29308	5.66838	2.83419	-9.31273	8.72658	-.103	3	.924

Ambulatory value Pre-IHG Training to Detraining – Dependent t-test

1a. 24-hour SBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre_IHG	134.7294	4	14.29104	7.14552
	Detraining	127.7488	4	8.98379	4.49189

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre_IHG - Detraining	6.98064	8.07569	4.03785	-5.86958	19.83087	1.729	3	.182

1b. 24-hour DBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre_IHG	83.3375	4	8.55798	4.27899
	Detraining	78.0137	4	3.65028	1.82514

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre_IHG - Detraining	5.32386	6.11844	3.05922	-4.41194	15.05966	1.740	3	.180

1c. 24-hour MAP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre_IHG	100.9559	4	8.43830	4.21915
	Detraining	95.0728	4	5.77430	2.88715

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre_IHG - Detraining	5.88308	4.49594	2.24797	-1.27097	13.03713	2.617	3	.079

1d. 24-hour HR:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre_IHG	63.9660	4	4.42377	2.21188
	Detraining	60.8874	4	5.14356	2.57178

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre_IHG - Detraining	3.07857	4.58993	2.29497	-4.22503	10.38218	1.341	3	.272

2a. Daytime SBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre_IHG	137.9430	4	13.00381	6.50190
	Detraining	131.9696	4	9.79517	4.89758

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre_IHG - Detraining	5.97333	6.93388	3.46694	-5.06002	17.00669	1.723	3	.183

2b. Daytime DBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre_IHG	87.0031	4	6.77739	3.38870
	Detraining	81.8860	4	4.55315	2.27658

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre_IHG - Detraining	5.11708	3.84522	1.92261	-1.00151	11.23568	2.662	3	.076

2c. Daytime MAP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre_IHG	104.5376	4	6.39980	3.19990
	Detraining	98.7285	4	6.82522	3.41261

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre_IHG - Detraining	5.80906	2.64885	1.32443	1.59415	10.02397	4.386	3	.022

2d. Daytime HR:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre_IHG	65.3413	4	4.77629	2.38814
	Detraining	62.4196	4	6.13395	3.06697

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre_IHG - Detraining	2.92171	5.48004	2.74002	-5.79826	11.64167	1.066	3	.364

3a. Nighttime SBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre_IHG	124.8507	4	17.94181	8.97091
	Detraining	115.1563	4	9.97046	4.98523

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre_IHG - Detraining	9.69444	12.12081	6.06040	-9.59246	28.98135	1.600	3	.208

3b. Nighttime DBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre_IHG	72.2986	4	12.51229	6.25614
	Detraining	66.7500	4	3.65006	1.82503

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre_IHG - Detraining	5.54861	10.53623	5.26812	-11.21688	22.31410	1.053	3	.370

3c. Nighttime MAP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre_IHG	90.4167	4	14.13792	7.06896
	Detraining	84.2902	4	5.17727	2.58863

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre_IHG - Detraining	6.12649	10.37462	5.18731	-10.38185	22.63483	1.181	3	.323

3d. Nighttime HR:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre_IHG	59.7292	4	4.87785	2.43892
	Detraining	56.8929	4	3.48014	1.74007

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre_IHG - Detraining	2.83631	3.86555	1.93278	-3.31465	8.98727	1.467	3	.239

4a. Dipping SBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre_IHG	9.7608	4	4.72622	2.36311
	Detraining	12.7503	4	3.42110	1.71055

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre_IHG - Detraining	-2.98947	6.47338	3.23669	-13.29007	7.31112	-.924	3	.424

4b. Dipping DBP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre_IHG	17.3333	4	7.65393	3.82697
	Detraining	18.4735	4	1.45434	.72717

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre_IHG - Detraining	-1.14015	8.59149	4.29575	-14.81114	12.53083	-.265	3	.808

4c. Dipping MAP:

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre_IHG	13.8611	4	7.89901	3.94951
	Detraining	14.5599	4	2.74886	1.37443

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	Pre_IHG - Detraining	-.69876	9.04178	4.52089	-15.08625	13.68872	-.155	3	.887

Relationship Between Baseline SBP and SBP Change Following IHG Training

Bivariate Correlation

Descriptive Statistics

	Mean	Std. Deviation	N
SBPChange	-6.0000	10.67708	4
BaselineSBP	134.2500	14.40775	4

Correlations

		SBPChange	BaselineSBP
SBPChange	Pearson Correlation	1	-.904
	Sig. (2-tailed)		.096
	N	4	4
BaselineSBP	Pearson Correlation	-.904	1
	Sig. (2-tailed)	.096	
	N	4	4

Effects of IHG Training on Resting and Ambulatory SBP
Repeated Measures ANOVA

1. Resting SBP:

Descriptive Statistics

	Mean	Std. Deviation	N
Pre_IHG	134.1667	14.47987	4
Post_IHG	128.2500	6.62417	4
Detraining	123.2500	14.92793	4

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[c]
Time	Pillai's Trace	.436	.773[b]	2.000	2.000	.564	.436	1.546	.086
	Wilks' Lambda	.564	.773[b]	2.000	2.000	.564	.436	1.546	.086
	Hotelling's Trace	.773	.773[b]	2.000	2.000	.564	.436	1.546	.086
	Roy's Largest Root	.773	.773[b]	2.000	2.000	.564	.436	1.546	.086

a. Design: Intercept
Within Subjects Design: Time

b. Exact statistic

c. Computed using alpha = .05

2. Ambulatory 24-hour SBP:

Descriptive Statistics

	Mean	Std. Deviation	N
Baseline	134.7294	14.29104	4
Week8	132.9256	8.73204	4
Week12	127.7488	8.98379	4

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[c]
Time	Pillai's Trace	.633	1.728[b]	2.000	2.000	.367	.633	3.455	.129
	Wilks' Lambda	.367	1.728[b]	2.000	2.000	.367	.633	3.455	.129
	Hotelling's Trace	1.728	1.728[b]	2.000	2.000	.367	.633	3.455	.129
	Roy's Largest Root	1.728	1.728[b]	2.000	2.000	.367	.633	3.455	.129

a. Design: Intercept

Within Subjects Design: Time

b. Exact statistic

c. Computed using alpha = .05

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