Investigating the effect of isometric handgrip training frequency on cardiovascular health in medicated hypertensives

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Submitted in partial fulfillment of the requirements for the degree of Master of Science in Applied Health Sciences (Health Sciences)

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© June 2018
Abstract

Hypertension (HTN) is expected to affect approximately 50% of the world’s adult population by 2025 and accounts for 10 million deaths worldwide each year. Historically, HTN has been defined as systolic blood pressure (SBP) greater than 140 mmHg and/or diastolic blood pressure (DBP) greater than 90 mmHg. However, it has been recently suggested that the risks of HTN begin at even lower BP levels and in the United States HTN is now defined as ≥130/80 mmHg. HTN increases the presence of many independent risk factors and/or indicators for cardiovascular disease (CVD) such as increased arterial stiffness and reduced cardiovagal baroreflex sensitivity (cvBRS). This study aimed to investigate the minimum training frequency necessary to maintain decreases in BP following an initial 8-week training period by training individuals 0, 1, or 3 times per week for 4 weeks. Sixteen individuals with medicated hypertension (age 65±9 years) were recruited and performed 8 weeks of IHG 3 times per week and were then allocated to one of 3 training frequency groups; 0, 1 or 3 times for a subsequent 4 weeks. Statistically significant decreases in SBP and DBP were observed in all participants following the initial 8-week IHG training program (-9±10mmHg, p=0.004; -5±6mmHg, p=0.006), as well as at 12 weeks (-9±10 p=0.047; -5±7, p=0.051). cvBRS did not demonstrate any significant changes, while carotid-toe pulse wave velocity (ctPWV), a measure of systemic arterial stiffness, demonstrated a significant main effect for time (p=0.002). Post-hoc testing revealed significant decreases in ctPWV at 12 weeks (-1.0±1.1, p=0.002), as well as a significant decrease from 8 to 12 weeks (-0.73±1.1, p=0.017). As for trained limb arterial stiffness, carotid-radial pulse wave velocity
(crPWV) demonstrated a significant effect for group (p=0.045) and time (p=0.015). Post-hoc testing revealed that there was no significant difference between groups, however there was a significant decrease in crPWV at 12 weeks (-1.4±1.7, p=0.010). These findings suggest that IHG at a training frequency lower than traditionally prescribed may maintain the decrease in SBP and DBP with the inclusion of improvements in arterial stiffness both systemically and in the trained limb over time. Thus, these results support the prescription of IHG in the treatment of HTN.

**Keywords:** Isometric handgrip training, medicated hypertension, blood pressure, arterial stiffness, baroreflex sensitivity
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III List of Acronyms

ABPM – Ambulatory blood pressure measurement
ACE – Angiotensin converting enzymes
ACC – American College of Cardiology
ACSM – American College of Sports Medicine
AE – Aerobic exercise
AHA – American Heart Association
ANOVA – Analysis of variance
ANS – Autonomic nervous system
AMS – Artery management system
AOBPM – Automated office blood pressure measurement
AOBPM – automated office blood pressure measurement
ARB – Angiotensin II receptor blocker
ATRAMI – Autonomic tone and reflexes after MI
AV – Atrioventricular
BMI – Body mass index
BP – Blood pressure
BPM – Beats per minute
BPV – Blood pressure variability
CAD – Coronary artery disease
CCA – Common carotid artery
CCB – Calcium channel blockers
cfPWV – Carotid-femoral pulse wave velocity
CHEP – Canadian Hypertension Education Program
cm – Centimetre
crPWV – Carotid-radial pulse wave velocity
CSA – Cross-sectional area
ctPWV – Carotid-toe pulse wave velocity
cvBRS – Baroreflex sensitivity
CVD – Cardiovascular disease
CVLM – Caudal ventrolateral medulla
DASH – Dietary approaches to stop hypertension
DBP – Diastolic blood pressure
DICOM – Digital Imaging and Communications in Medicine
FFT – Fast Fourier Transform
HBPM – home blood pressure measurement
HCP – Healthcare practitioner
HF – High frequency
HR – Heart rate
HRV – Heart rate variability
HTN – Hypertension
Hz – Hertz
ICA – Internal carotid artery
IHG – Isometric handgrip training
ILE – Isometric leg exercise
KG – Kilogram
LDmax – Maximum lumen diameter
LDmin – Minimum lumen diameter
LF – Low frequency
M – Metre
MAP – Mean arterial pressure
MI – Myocardial infarction
mm – Millimetre
mmHg – Millimetres of mercury
ms – Millisecond
MSNA – Muscle sympathetic nerve activity
MVC – Maximum voluntary contraction
NTS – Nucleus tractus solitarius
OBPM – Office blood pressure measurement
PNS – Parasympathetic nervous system
PP – Pulse pressure
PSD – Power spectral density
PWTT – Pulse wave transit time
PWV – Pulse wave velocity
Q – Cardiac output
RCT – Randomized controlled trial
RE – Resistance exercise
ROS – Reactive oxygen species
RRI – R-R interval
RVLM – Rostral ventrolateral medulla
SA – Sinoatrial
SBP – Systolic blood pressure
SD – Standard deviation
SNS – Sympathetic nervous system
TPR – Total peripheral resistance
VO₂ Max – Maximal oxygen consumption
WHR – Waist-to-hip ratio
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1 INTRODUCTION

1.1 General Context

Hypertension (HTN) has traditionally been defined as resting blood pressure (BP) \( \geq 140/90 \) mmHg. Recent reports have suggested that the risks of HTN begin at \( \geq 130/80 \) mmHg (Whelton et al., 2017). HTN accounts for 9.4 million deaths worldwide annually (Lim et al., 2012) and is predicted to continue to afflict more than 50% of the world’s adult population by 2025 (Kearney et al., 2005). Although HTN is the most common modifiable risk factor for cardiovascular disease (CVD), it is not adequately managed by many individuals (Sarafidis et al., 2011). Of those who seek pharmacological therapy, 14% become resistant to treatment within 5 years, leaving them at a 50% greater risk for adverse cardiovascular events (Benjamin et al., 2017). Research has consistently linked high BP with poor test scores of non-invasive autonomic function indices such as heart rate variability (HRV) (Parati & Esler, 2012) and cardiovagal baroreflex sensitivity (cvBRS) (La Rovere, 2008). In fact, those with HTN often experience blunted cvBRS (Bristow et al., 1969). Likewise, individuals with HTN have stiffer arteries that are unable to stretch and activate the baroreceptor reflex to modulate subtle changes in BP (Milic et al., 2009). In fact, evaluation of arterial stiffness and cvBRS are important non-invasive indicators of present and future cardiovascular health (La Rovere, 2008).

Resistant HTN, defined as BP \( \geq 140/90 \) mmHg despite adhering to a regime of at least 3 BP medications, including a diuretic at the maximum tolerated dosage (Alderman, 2008), is particularly troublesome as this type of high BP does not respond to traditional interventions such as drugs, diet and aerobic exercise. However, a novel exercise regime,
known as isometric handgrip (IHG) training, has been introduced and shown to induce clinically significant decreases in BP after as little as 8 weeks of training (Millar et al., 2013). Isometric handgrip training studies tend to use a handgrip dynamometer programmed to maintain forearm muscle contraction at 30% of maximum voluntary contraction (MVC) for 2 minutes, 2 sets per hand performed 3 times per week for 8 weeks. This protocol has been used extensively in the literature to produce decreases in BP among populations with normotension (McGowan et al., 2007; Somani et al., 2018; Badrov et al., 2016), hypertension (Taylor et al., 2003; Carlson et al., 2016) and medicated hypertension (Millar, 2013; Badrov et al., 2013b). The greatest effects have been seen among hypertensive populations, particularly among those with the highest BP (Millar et al., 2007). As a result, this training protocol is endorsed by both the Canadian Hypertension Education Programme (2017) and the American College of Cardiology (ACC)/ American Heart Association Task Force on Clinical Practice Guidelines (AHA) (2017) for the treatment of HTN.

While the frequency of and length of training required to induce optimal changes in BP have been suggested to be 3 times per week over a period of eight to ten weeks (Badrov, 2013a; Leung et al., 2017), no such study has looked in-depth into the effects of detraining following IHG intervention. It was noted that hypotensive effects of IHG training were lost following only 7-10 days of abstinence from training (Millar, 2007). Therefore, investigation into the minimum training frequency required to maintain the hypotensive benefits gained from the traditional 8-week IHG training regimen is necessary. Additionally, IHG training studies have demonstrated varied results regarding improvements in autonomic control, measured by HRV and blood pressure variability.
(BPV), among populations with diverse BP levels. (Millar, 2007; Stiller-Moldovan, 2012; Taylor, 2003). While other measures, such as local endothelial function, (i.e. flow mediated dilation), have been found to improve following 8 weeks of training (McGowan et al., 2006a; McGowan et al., 2006b; Badrov et al., 2016). However, this improvement in local dilation did not appear to be associated with vasculature changes, nor changes in systemic endothelial function (McGowan et al. 2007; McGowan et al., 2006a), yet measures of arterial stiffness, such as carotid-femoral and carotid-ankle pulse wave velocity (PWV) have been shown to acutely increase following a bout of IHG training in both populations with HTN (Moon et al., 2015) and normotension (Davies et al., 2007), respectively. As well, further investigation regarding changes in autonomic function and arterial stiffness is warranted.

This study investigated the effects of IHG training and detraining on resting BP, arterial stiffness and cvBRS among individuals with medicated hypertension. This study hoped to provide sufficient information regarding the frequency of training necessary to maintain decreases in BP following an initial 8-week training period. Furthermore, this study aimed to investigate cvBRS and arterial stiffness as potential mechanisms contributing to the reduction in BP elicited by IHG training. Ultimately, it is hoped that by improving our understanding of this intervention it can be implemented into the standard of care for Canadians living with HTN.

1.2 Purpose of Research

The purpose of this study was to determine if there were reductions in resting BP, and alterations in cvBRS and arterial stiffness in those medicated for HTN following 8 weeks of IHG training consisting of 2 sets of 2-minute isometric contractions per hand 3
times per week. This study also aims to investigate the minimum training frequency necessary to maintain decreases in BP following the initial 8-week training period by training individuals 0, 1, or 3 times per week for 4 weeks.

2 Literature Review

2.1 Blood pressure

Arterial BP can be defined as the pressure exerted by blood on vessel walls (Pickering et al., 2005) and is the product of cardiac output (Q), the amount of blood pumped by the heart, and total peripheral resistance (TPR), the resistance of the arterial system to blood flow (Brzezinski, 1990). Systolic blood pressure (SBP) is the force placed on the arterial wall when the left ventricle contracts. Diastolic blood pressure (DBP) is the pressure exerted on the arterial wall when the ventricle relaxes (Klabunde, 2012). Typically, BP is expressed as SBP/DBP and is measured in mmHg, a unit of pressure. BP can also be expressed as mean arterial pressure (MAP), the weighted average of systolic and diastolic pressures. Pulse pressure (PP) is the difference in pressure between systolic and diastolic pressure and represents the impact that ventricular contraction has on the arterial system (O’Rourke, 1990).

Traditionally, BP values have been categorized as: normotension (SBP <120 mmHg and DBP <80 mmHg), prehypertension (SBP 120-139 mmHg and/or DBP 80-89 mmHg), stage I HTN (SBP 140-159 mmHg and/or DBP 90-99 mmHg), and stage II HTN (SBP >160 and/or DBP >100 mmHg) (Carretero & Oparil, 2000). Recently, a new lower classification system for HTN has been adopted in the United States (≥130/80 mmHg),
citing that the deleterious effects of elevated BP begin at an even lower value than previously thought (Whelton et al., 2017).

BP screening is vital for the diagnosis of HTN. Accurate assessment of BP allows for proper diagnosis, precise cardiovascular risk assessment, the assessment of appropriate interventions and their effects (Chesterton et al., 2013). BP screening frequency is at the discretion of the healthcare provider, but tends to hinge on the severity of the condition.

2.2 Blood Pressure Measurement Methods

There are 4 approaches that can be taken to assess BP: non-automated office measurement (OBPM), automated office measurement (AOBPM), ambulatory measurement (ABPM) or home monitoring (HBPM). Each method has its own strengths and weaknesses.

2.2.1 Manual Blood Pressure Measurements

The first BP measurement method is the manual, auscultatory method or non-automated OBPM. OBPM is measured by a trained practitioner using a mercury sphygmanometer together with an inflatable arm bladder and stethoscope. For measurements using the auscultation method, the bladder should be appropriately matched to the size of the arm; bladder length should cover 80-100% of the arm circumference and the width should be close to 40% arm circumference (Leung et al., 2017). The bottom edge of the cuff should be placed 3 cm above the elbow crease with the bladder centered over the brachial artery. The arm should be bare and supported at heart level (Leung et al., 2017). The patient should rest quietly for 5 minutes prior to measurement with both feet flat on the floor and legs uncrossed (Leung et al., 2017). It is
recommended to measure BP in both arms using the arm with the higher measurement for all subsequent measurements, keeping it consistent between visits to monitor changes. It is recommended to leave at least 1-minute between readings and to minimize the amount of time the cuff is inflated as not to congest the venous system making sounds more difficult to hear. The first reading should be discarded and the latter two averaged. The accepted practice to assess BP using the auscultation method is as follows: place the bell of a stethoscope over the brachial artery, increase the pressure of the cuff to 30 mmHg above the level at which the radial pulse is extinguished, deflate the cuff at a rate of 2 mmHg per heartbeat (Leung et al., 2017). The systolic value is read when there is the first occurrence of a clear tapping sound (phase I Korotkoff) and the diastolic value is read when the sound disappears (phase V Korotkoff). If Korotkoff sounds persist as the level approaches 0 mmHg then the point of sound muffling (phase IV) is used to indicate diastolic pressure. BP is recorded to the nearest 2 mmHg (Leung et al., 2017). HTN is diagnosed by this method when SBP is >140 mmHg and/or DBP is >90 mmHg (Leung et al., 2017).

2.2.2 Automated Office Blood Pressure Measurements

AOBPM use BP oscillations to detect SBP and DBP. The BP oscillations are high pass filtered to extract the oscillations at the cardiac frequency (Babbs, 2012). The oscillations increase in size between systolic and MAP, then decrease in size between MAP and DBP. The point of maximal oscillation amplitude corresponds to MAP and from there SBP and DBP estimates are calculated. SBP is found at 50% of the rising phase of the oscillation and DBP is found at 70% of the descending phase (Babbs, 2012).
AOBPM aims to reduce 3 common errors associated with manual BP measurements. These errors are participant-related, observer error and observer-participant interaction (Myers et al., 2006). Examples of participant-related error can include poor posture during measurement, talking during measurement or excessive movement (Myers et al., 2006). Examples of observer error include rounding BP to a near digit, deflating the cuff too quickly or failing to choose an appropriate cuff size (Myers et al., 2006). Observer-participant error is most commonly referred to as White-Coat HTN (see section 2.2.5.1). The use of an automated BP cuff can bypass these issues by removing the human interaction associated with auscultation methods, decreasing SBP by up to 9 mmHg and DBP by 6 mmHg in clinical practice (Leung et al., 2016).

The AOBPM method is where a practitioner will measure BP with an automated oscillometric device programmed to take measurements at regular intervals while the practitioner is absent. The practitioner will use an appropriately sized cuff as directed by the manufacturer and monitor known to be valid (Leung et al., 2017). The practitioner will apply the cuff with the lower edge 3 cm above the elbow crease and the bladder centered over the brachial artery. The cuff should be applied on a bare arm supported at heart level. Measurements are done seated with feet flat on the floor and legs uncrossed with no talking for the duration of measurement (Leung et al., 2017). The practitioner will take the first measurement to assure accurate cuff placement and validity of the measurement. All subsequent measurements will be automatically taken at 1-2 minute intervals with the practitioner absent. Devices such as the BpTRU (VSM MedTech Ltd, Vancouver, Canada) take 6 measurements, discard the first and average the results of the latter 5. The practitioner will record the HR and the average BP recorded by the device.
HTN is diagnosed by this method when the mean SBP displayed is >135 mmHg and the DBP is > 85 mmHg (Leung et al., 2017).

2.2.3 Ambulatory Blood Pressure

ABPM is an oscillometric BP measurement which allows for the measurement of BP over a 24-hour period. ABPM is the preferred method of out-of-office BP measurement. ABPM is required when an office-induced increase in BP is suspected. ABPM is also indicated for individuals who experience persistently elevated BP despite receiving an optimal regime of antihypertensive therapy, individuals with symptoms of hypotension and fluctuating BP readings in-office (O’Brien et al., 2013).

In order to assess 24-hour BP, a cuff is applied to the non-dominant arm, unless there is a >10% difference in SBP between the arms in which case the cuff will be applied to the arm with greater BP. The cuff should fit as described in previous sections. The device should be programmed to record for a minimum of 24 hours with the measurement frequency set at 20-30 minute intervals during the day and 30-60 minute intervals at night (Pickering et al., 2006). Daytime and nighttime activities, symptoms and medication administration are to be recorded in a diary to better interpret data. Daytime and nighttime should be defined using the diary (i.e. sleep and wake times) or pre-determined thresholds may be used (i.e. 8 am to 10 pm for daytime and 10 pm to 8 am for nighttime) (Fagard et al., 1997). The ambulatory monitor will report all of the BP readings, the percentage of successful readings, the averages for each collection period and the percent change in BP from daytime to nighttime (dipping percentage). The criteria for a successful ABPM collection period is at least 70% of readings being successful, at least 20 successful daytime readings and at least 7 successful nighttime
readings. HTN is diagnosed if the mean awake SBP is >135 mmHg or the DBP is >85 mmHg, or if the mean 24-hour SBP is >130 mmHg or the DBP is >80 mmHg (Leung et al., 2017)

ABPM measurement allows for a realistic view of how BP behaves outside a clinical setting, which can be inflated in many individuals since BP is a dynamic measure and sensitive to emotional stress. ABPM also allows for BP readings overnight, which is a useful prognostic tool for cardiovascular risk factors (Fagard et al., 2008). Since ABPM can be used overnight it serves as a valuable tool in determining if individuals with HTN experience BP dipping. In healthy individuals BP decreases by 10-20% at night (Routledge et al., 2007). However, in individuals with HTN, this decrease is not always present (Pickering et al., 2001). Individuals can be categorized into groups by their ratio of daytime SBP to nighttime SBP: extreme dippers (night/day BP ratio ≤ 0.8), dippers (0.8 < ratio ≤ 0.9), non-dippers (0.9 < ratio ≤ 1.0) and reverse dippers or risers (ratio > 1.0). Individuals who experience non-dipping or reverse dipping display elevated nighttime sympathetic activity and decreased parasympathetic activity (Fagard, 2009). Evidence suggests that individuals with HTN experiencing non-dipping or reverse dipping are more likely to experience left ventricular hypertrophy, elevated left ventricular mass index, carotid artery wall thickening, carotid artery atherosclerotic plaques, cerebral infarct and stroke (Routledge et al., 2007).

2.2.4 **Home Blood Pressure Measurement**

HBPM has been offered as an alternative to ABPM to aid in the diagnosis of HTN. HBPM is indicated for individuals who have diabetes mellitus chronic kidney disease, suspected non-adherence to lifestyle modification and/or pharmacological
intervention, demonstrated white-coat effect (described in section 2.2.5.1), and/or masked HTN (described in section 2.2.5.2) (Mancia & Parati 2011). Home BP measurement can be used when ABPM is not available, not tolerated or the individual prefers this type of measurement (Campbell et al., 2001). HBPM should occur using a validated electronic device such as the Omron device (Omron Healthcare, HEM-780 CANN, Illinois, USA). This device should be sized with an appropriately sized bladder close to 40% of the arm circumference and the length should cover 80-100% of the arm circumference or as recommended by the manufacturer. Measurements should occur on the non-dominant arm unless there is a >10 mmHg difference in SBP between arms, in which case the arm with the higher BP should be measured. BP measurement should occur following 5 minutes of silent rest with both feet flat on the floor, back supported and arm supported at heart level (Leung et al., 2017). Measurements should be performed twice before breakfast and twice 2 hours after dinner for 7 days and the values recorded. BP averages are calculated as the average of 24 measurements taken over 6 days, excluding the first day’s readings. Measurements should occur prior to taking any medication and a minimum of 30 minutes following caffeine or tobacco consumption or 30 minutes post-exercise (Stergiou et al., 1998).

HTN can be diagnosed by HBPM when SBP >135 mmHg or DBP >85 mmHg. If the office BP measurement is high and home BP measurement is <135/85 mmHg, it is recommended to either repeat the HBPM or perform ABPM to confirm that 24-hour BP is <130/80 mmHg and the mean awake BP is <135/85 mmHg before confirming white-coat HTN. Home SBP >135 and DBP >85 are considered elevated and are associated with greater overall cardiac mortality risk (Tsuji et al., 1997; Sakuma et al., 1997).
2.2.5 **Hypertension**

HTN is estimated to effect 1 billion people worldwide, and is projected to increase as the population ages (WHO, 2013). HTN is the number one risk factor for adverse cardiovascular events (Kannel, 2009) and is an established risk factor for myocardial infarction, stroke, and heart failure (Chobanian, 2003). The main predictors of HTN are obesity, insulin resistance, high alcohol intake, high salt intake and aging (Chobanian et al., 2003), each of which are also linked to increased risk of adverse cardiovascular events (Staessen et al., 2003).

Specifically, beginning at a BP of 115/75 mmHg, the risk of CVD doubles with each increment of 20/10 mmHg (Franco et al., 2004). In a study on the predictive value of home BP measurement, each 10 mmHg increase in SBP resulted in a 17.2% increase in the risk of a cardiovascular event (Bobrie et al., 2004). Similarly, a meta-analysis of 30 clinical trials concluded that a 5 mmHg reduction in SBP lowered the risk of a cardiovascular event and stroke by 25% and 30%, respectively (Staessen et al., 2003). Finally, a reduction in DBP of 5 mmHg is associated with a 34% less chance of stroke and a 21% less chance of coronary heart disease (McMahon et al., 1990).

There are two main forms of HTN: primary HTN and secondary HTN. Primary HTN is not attributed to a clear cause, but can be linked to poor diet, genetics, obesity and inactivity (Mokdad, 2003; see below for more detail). Conversely, secondary HTN can be attributed to other medical conditions (e.g. coarctation of the aorta, Cushing syndrome, pheochromocytoma) (Viera et al., 2010).

Essential HTN non-modifiable risk factors include psychosocial stress, premature birth and low birthweight, chronic kidney disease, family history, age, low
socioeconomic status, male sex and obstructive sleep apnea (Whelton et al., 2017). Modifiable risk factors include high sodium intake, low potassium intake, excessive alcohol intake, smoking, diabetes mellitus, high cholesterol, body mass, physical inactivity and dietary habits (Yusuf et al., 2004).

The main mechanisms proposed to contribute to the development of HTN are excess fluid retention (Hwang et al., 2017), chronic activation of the renin-angiotensin-aldosterone system (RAAS) (Te Riet et al., 2015), chronic SNS activation (Grassi et al., 2015), and arterial stiffness (Humphrey et al., 2016).

The first proposed contributor to HTN is excess fluid retention. The exact mechanism causing chronic excess fluid retention is unclear, however chronic kidney disease, obesity and hyperaldosteronism are likely involved (Schriffin et al., 2007; Hall et al., 2015; Te Riet et al., 2015). In the presence of fluid retention and the inability to increase sodium excretion, excessive salt intake exacerbates existing fluid retention in an attempt to maintain homeostasis. Increased fluid retention thereby increases blood volume and BP. Some research has suggested individuals who develop HTN may be particularly sensitive to increased salt intake (Feng et al., 2017).

Chronic kidney disease can contribute to increased sodium and fluid retention due to impaired renal pressure natriuresis (Khajawa & Wilcox, 2011). Renal pressure natriuresis is a mechanism which decreases sodium resorption when renal perfusion pressure is high (Ivy & Bailey, 2014). Individuals with HTN have ineffective pressure natriuresis allowing for higher levels of BP to be maintained. It has been found that decreased functioning of the nephrons may inhibit the ability to excrete excess sodium, and promote the retention of sodium (Briet & Schriffin, 2010).
Similarly in the case of obesity, renal pressure natriuresis is impaired. First, obese individuals tend to have dysfunctional natriuretic peptides, which impair the ability of the kidneys to maintain appropriate fluid balance (Hall et al., 2015). Second, obesity increases visceral and retroperitoneal fat. This type of fat distribution surrounds the midsection and engulfs the organs (Kovesdy et al., 2017). These fat deposits compress the kidneys and increase intra-renal pressure potentially impairing renal pressure natriuresis and causing activation of the RAAS impairing fluid balance (Hall et al., 2015).

Kidney-secreted RAAS hormones play an important role in BP and vascular homeostasis. Angiotensin II promotes vasoconstriction in the arterioles and promotes sodium and fluid retention (Te Riet et al., 2015). Both chronic kidney disease and obesity have been associated with increased RAAS activation, leading to chronically increased fluid volume (Borrelli et al., 2013; Hall et al., 2015). Another RAAS hormone, aldosterone is a mineralocorticoid secreted in response to angiotensin II which increases the reuptake of sodium and water in the kidneys (Te Riet et al., 2015). In addition to increasing blood volume, aldosterone has also been shown to have direct effects on the vasculature promoting inflammation, arterial stiffening and oxidative stress which may contribute to the vascular endothelial dysfunction seen in HTN (Te Riet et al., 2015).

Furthermore, the brain’s RAAS pathways may contribute to the development of HTN. In contrast to RAAS hormones secreted by the kidneys, the RAAS system in the brain becomes upregulated with increased sodium loading through a positive feedback loop promoting further sodium retention (Takahashi et al., 2012). In response to increased angiotensin II secreted from the brain, aldosterone secretion also increases, increasing renal SNS activity (Grassi et al., 2015). Renal SNS activity reduces blood flow
to the kidneys and increases renal sodium resorption, while chronic SNS activation has other effects in the body.

The development and maintenance of HTN has been thought to be partly due to augmented SNS activation. In HTN individuals, SNS activity and norepinephrine spillover (a SNS neurotransmitter) from the kidneys has been found to be higher compared to normotensive individuals (Grassi et al., 2015). As well, increased renal nerve activity through sympathetic activation may further increase renal tubular sodium reabsorption, in turn increasing renin secretion and circulating angiotensin II (DiBona, 2013). Other HTN comorbidities associated with increased SNS activity include obesity, obstructive sleep apnea, chronic kidney disease and insulin resistance (Le Jemtel et al., 2017; Grassi et al., 2015; Esler 2014).

Whether arterial stiffness is a cause or a consequence of HTN is still being investigated, however the two are closely linked (Mitchell, 2010). Proposed contributors to HTN-associated increases in arterial stiffness include increased sympathetic tone, circulating aldosterone, aging and comorbidities (i.e. diabetes, obesity) (Humphrey et al., 2016).

As for secondary HTN, it makes up only 5-10% of HTN diagnoses (Camelli et al., 2015). Conditions such as diabetic nephropathy, renovascular HTN, pheochromocytoma or coarctation of the aorta can cause secondary HTN. Secondary HTN differs from primary (essential) HTN as the onset is much faster and more severe and occurs outside the normal age range for the onset of primary HTN (before 30 years and after 55 years of age). Additionally, secondary HTN is easier to treat as there is a clear cause of BP
elevation and treating the underlying cause generally lowers BP. Primary HTN is more difficult to treat as there may be a myriad of underlying causes (Staessen et al., 2003).

2.2.5.1 White-Coat Hypertension

White-Coat HTN is the disparity of >20 mmHg SBP and/or >10 mmHg DBP between an out-of-office BP measurement and an in-office BP measurement (Pickering, 2005). BP is a dynamic measurement, subject to variation due to many factors. Individuals may feel stressed about having a healthcare provider measure their BP in a clinical setting, and so BP may increase to values higher than BP measured at home (Siegel et al., 1990). This phenomenon is known as White-Coat HTN. Documentation of White-Coat HTN requires a reliable assessment of out-of-office BP values. In fact, 15-20% of individuals diagnosed with stage-I HTN may only be elevated in the presence of a healthcare provider (Pickering et al., 2005).

White-Coat HTN has been shown to be minimized when physician contact is minimal (Myers et al., 2012). This brings about the necessity of different types of BP measurements which can potentially minimize the doctor-patient interaction and thereby reduce the White-Coat effect. Among individuals who present with White-Coat HTN, practitioners should opt for ABPM as the preferred out-of-office measurement, or AOBPM as the preferred in-office measurement to accurately assess BP status as these measurements decrease physician contact (Cobos et al., 2015)

2.2.5.2 Masked Hypertension

Masked HTN presents as lower BP (SBP <140, DBP <90) during in-office visits, but elevated outside the clinic setting (daytime ABPM or HBPM measurement SBP >135, DBP >85) (Pickering et al., 2007). Masked HTN is particularly troublesome as it can go
undiagnosed and untreated for a long period of time leaving the patient at an elevated risk of CVD. A study by Trudel and colleagues in 2009 found among a cohort of 2970 white-collar workers that 15% of the participants had elevated daytime ambulatory BP, indicative of masked HTN. Men were over twice as likely to suffer from masked HTN compared to women. Among men the chances of presenting with masked HTN increased with increasing age (45 plus years) and body mass index (BMI). Among women the chance of presenting masked HTN were increased by BMI and alcohol intake (> 6 standard drinks per week) (Trudel et al., 2009). A study performed by Hanninen et al., in 2011 echoed the results of Trudel et al., finding that alcohol consumption, BMI, sex and age all contributed to the risk of masked HTN. However, this research team also found that smoking, alongside concomitant health problems such as left ventricular hypertrophy and diabetes contributed to the risk of masked HTN. Interestingly, masked HTN independently correlated with hypochondria, an anxiety disorder. The presence of undetected HTN necessitates at-home monitoring among individuals with risk factors for HTN, in addition to those who present with high-normal BP.

### 2.2.5.3 Resistant Hypertension

Resistant HTN can be defined as BP $\geq 140/90$ mmHg, or SBP $\geq 140$ mmHg, despite adhering to a regime of three classes of anti-HTN drugs at the maximum dosage, one of which is a diuretic (Calhoun et al., 2008). Resistant HTN has also been defined as BP 120/80 mmHg while taking four or more anti-HTN drugs at the maximum dosages (Chobanian et al., 2003). BP tends to remain resistant due to persistently elevated SBP (Black, 2004). The strongest predictors of resistant HTN are age and obesity (Calhoun, 2008). Individuals $>75$ years are only 25% as likely to have controlled SBP as individuals
<60 years (Judd & Calhoun, 2012). Individuals who are obese (BMI >30 kg/m²) only have a 33% likelihood of their BP being controlled compared to lean individuals (BMI <25 kg/m²) (Lloyd-Jones et al., 2002). The definition of resistant HTN excludes individuals not taking anti-hypertensive medications, those with poor medication adherence or white-coat HTN (Calhoun et al., 2008).

2.2.6 Hypertension Diagnosis

The primary method for diagnosing HTN, as described in section 2.2.1, has been by OBPM. OBPM is performed by auscultation using a manual BP cuff in a doctor’s office. Diagnosis for HTN using this method is SBP > 140 mmHg or DBP >90 mmHg, and pre-HTN is SBP 130-39 mmHg or DBP 85-89 mmHg. However, these readings tend to be higher than AOBPM due to failure in following standardized methodological practice, reading 9/6 mmHg higher on average (Myers et al., 2009). This can lead to inaccuracies in BP measurement and misclassification of cardiovascular risk. For these reasons, in recent years AOBPM has become common practice (see section 2.2.2). In patients presenting with hypertensive urgency or emergency, they are diagnosed and treated immediately. In all other patients two or more measurements should be taken (Leung et al., 2017).

If AOBPM or OBPM in visit 1 is SBP >180 mmHg and/or DBP >110 mmHg, HTN is diagnosed. If visit 1 AOBPM SBP is 135-179 mmHg and/or DBP is 85-109 mmHg or the mean OBPM SBP is 140-179 mmHg and/or DBP is 90-109 mmHg, out-of-office BP measurements should be performed before visit 2, preferably ABPM when available and tolerated. The accepted practices for ABPM are presented in section 2.2.3. Also, medical history and physical assessment should be conducted and the potential for
end-organ damage clinical tests should be performed within 2 visits. The next visit should be scheduled within 1 month and exogenous factors elevating BP should be identified and reduced. However, if visit 1 SBP measurement by AOBPM is 130-139 mmHg and/or DBP 85-89 mmHg, annual follow-up is recommended (Leung et al., 2017).

In addition, if the patient with HTN is actively modifying their lifestyle factors, they should be followed up at 3-6 month intervals, or shorter (1-2 months) if the patient has more severe HTN. Patients receiving antihypertensive drug therapy should be seen every 2 months or less, depending on drug tolerance, target organ damage, severe HTN or symptomatology. These visits should occur regularly until 2 consecutive measurements are at target BP level (Leung et al., 2017).

2.3 **Lifestyle and Antihypertensive Treatment**

Current antihypertensive treatments combine both lifestyle and pharmacological elements. Lifestyle interventions include weight loss, low-sodium diets, reduced alcohol intake and the implementation of physical activity.

2.3.1 **Exercise**

Physical activity is associated with a 35% reduction in CVD mortality and a 33% reduction in all-cause mortality in comparison to individuals who engage in a sedentary lifestyle (Nocon et al., 2008). Among both individuals with HTN looking to decrease their BP and individuals with normotension looking to maintain their BP, recommendations for physical activity include 90-150 minutes of aerobic and/or dynamic resistance training and/or 3 sessions of isometric resistance exercise per week (Whelton
et al., 2017). A complete review of literature associated with the effects of exercise training can be found in section 2.6.

2.3.2 **Dietary Intervention**

To prevent HTN and reduce BP in individuals diagnosed with HTN, individuals are directed to follow the Dietary Approaches to Stop Hypertension (DASH) diet. The DASH diet was introduced more than 20 years ago and has shown efficacy in lowering BP among normotensive, pre-hypertensive and is especially effective in hypertensive populations (Appel et al., 1997). The DASH diet is rich in fruit and vegetables, low-fat dairy products, whole grains rich in dietary fibre and protein from plant sources with low saturated fat and cholesterol. The diet also suggests that individuals with HTN, and those who are at risk of developing HTN should lower sodium consumption to below 2000 mg per day. For those who are not at risk for hyperkalemia, dietary potassium supplementation can be implemented to further decrease BP. As well, alcohol intake should also be limited to <2 drinks per day, consumption should not exceed 14 standard drinks per week for men and 9 for women (one standard drink is considered 17.2 mL ethanol or approximately 44 mL 80 proof spirits, 355 mL 5% beer or 148 mL 12% wine) (Steinberg et al., 2017).

2.3.3 **Pharmacological Intervention**

In addition, antihypertensive medications may be prescribed. Antihypertensive therapy should be prescribed for individuals with an average SBP >160 mmHg and/or DBP >100 mmHg in the absence of macrovascular target end organ damage or other cardiovascular risk factors. In individuals with evidence of macrovascular target end
organ damage or other independent cardiovascular risk factors the criteria is lower (SBP >140 mmHg and/or DBP >90 mmHg) (Schmeider et al., 2010).

The most commonly prescribed BP medications include diuretics, beta-blockers, angiotensin converting enzymes (ACE) inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs) and various types of peripheral vasodilators. Each drug has a unique mechanism which acts to decrease BP through the vasodilation of vascular smooth muscle cells and/or a decrease in Q.

Diuretics act to decrease BP by decreasing blood volume and Q, resulting in a decrease in TPR (Pitts & Sartorious, 1950). β-blockers interfere with the binding of norepinephrine to β-adrenergic receptors, thus blocking sympathetic input resulting in negative chronotropic and inotropic effects on the heart, thereby decreasing Q and BP (Gorre et al., 2010). ACE inhibitors prevent the conversion of angiotensin I to angiotensin II, which is the active form of the hormone (Dzau, 1990). The decreased concentration of angiotensin II promotes renal excretion of sodium and water, decreasing blood volume and thus TPR. Additionally, decreased angiotensin II promotes vascular relaxation by decreasing aldosterone and catecholamine release, thereby decreasing sympathetic input. ACE inhibitors decrease the concentration of bradykinin in arteriolar smooth muscle, leading to vasodilation. ARBs block angiotensin II from binding to receptors in arterial and venous smooth muscle and cardiac muscle reducing contraction and leading to vasodilation (Reid, 1992). Furthermore, ARBs block the effect of angiotensin II in the kidneys, promoting the excretion of salt and water, as well as block sympathetic stimulation and aldosterone secretion from the pituitary gland (Ghiadoni et al., 2000). CCBs inhibit the uptake of calcium into the excitable pacemaker cells of the
heart and arterial smooth muscle cells causing decreased inotropic and chronotropic effects, as well as arterial vasodilation in addition to a diuretic effect at the kidneys (Katz, 1986). As for peripheral dilators, α-blockers can be divided into two classes, that of α1-blockers and α2-blockers. α1-blockers bind to α1-adrenergic receptors in the veins and arteries to block the binding of norepinephrine, causing vasodilation (Nash, 1990). α2-receptors are located in smooth muscle tissue (Lee, 1990). Therefore α2-receptor blockers decrease sympathetic input to the smooth muscle, thereby inducing vasodilation (Nash, 1990).

In some instances, HTN cannot be managed with one class of anti-hypertensive drug and often medications are combined. Upwards of two thirds of individuals with HTN cannot control their BP with only one anti-hypertensive medication (Chobanian et al., 2003). The ALLHAT study found that 60% of individuals with HTN whose BP was controlled (i.e. <140/90 mmHg) required two or more different classes of BP medications to manage their BP, while only 30% were able to manage their BP with only one medication (Cushman et al., 2002).

The most obvious factor which may contribute to persistently elevated BP is suboptimal treatment. This may present as overly conservative dosing of antihypertensive agents or inappropriate drug combinations on behalf of the physician (Levy et al., 2016). As well, other substances which may be used for concomitant disease or recreational use may contribute to persistently elevated BP. Agents such as tobacco use, alcohol consumption in excess, and use of illicit substances such as amphetamines and cocaine can contribute to an elevation in BP. Even prescribed medications for concomitant disease may have unfavourable interactions with antihypertensive medications (Munger
et al., 2007). However, one of the largest factors which may lead to poor BP response to antihypertensive intervention is lack of adherence (Ramli et al., 2012). In order to help a patient improve their medication regime several strategies may be employed to facilitate better adherence. The first method is to simply tailor the medication regime around the patient’s schedule to facilitate easier dosing. This may entail combining doses to once-a-day therapy or simplify the dosing by combining multiple medications into one pill (single pill combination) or using unit-of-use packaging for medications that cannot be combined (Conn et al., 2015). Additionally, giving a patient the liberty to be involved in their treatment can be beneficial and give them a sense of autonomy, potentially increasing their likelihood to adhere to pharmacological intervention. For example, patients can be encouraged to monitor their own BP and adjust their own medications. Furthermore, educating family members about their disease and treatment may aid to bolster support (Vrijens et al., 2017).

From a clinical perspective, BP management should involve assessing both pharmacological and lifestyle modification adherence at each office visit. Adherence can be encouraged with out-of-office contact such as phone calls or by mail while the patient is still adjusting to a new regime (i.e. first 3 months of treatment). Another method that can be employed is to work with pharmacists and work-site healthcare providers to improve monitoring of intervention adherence. Methods such as blister packs may help patients be more mindful of taking their medications and provide healthcare professionals with another method to monitor intake (Matthes et al., 2014). Additionally, patients can be reminded to take their medications as well as log their adherence by using electronic medication adherence aids (Fulmer et al., 1999).
In taking the proper steps to prevent and treat HTN including lifestyle modifications, such as exercise and dietary intervention, as well as anti-hypertensive pharmacotherapy, individuals also improve a number of non-invasive indices that are predictive of CVD risk. One marker in particular is that of cvBRS, a measure of cardiovascular autonomic function.

2.4 Cardiovagal Baroreflex Sensitivity

2.4.1 Arterial Baroreflex

The arterial baroreflex is a negative feedback loop the body uses to maintain BP within a narrow range (Saint Martin et al., 2013). The arterial baroreflex uses baroreceptors located in the aortic arch and carotid sinus to detect changes in BP (Kirchheim, 1974). Baroreceptors are mechanoreceptors, sensory neurons excited by changes in shape. In this case the stimulus is the deformation of the blood vessel in response to changes in BP. When BP increases the artery stretches thereby activating the baroreceptors, causing the release of an action potential to the central nervous system which responds appropriately to the input stimulus. Factors that play a role in BP homeostasis are Q and TPR (Gribbin et al., 1971).

The carotid sinus and aortic arch baroreceptors are innervated by the sinus nerve (nerve of Hering) and the aortic nerve, respectively. The nerves innervating the baroreceptors converge on the vagus nerve and travel up to the brain where they synapse on the nucleus tractus solitarius (NTS) (Benarroch, 2009). When the baroreceptors sense an increase in BP, more frequent signals are sent to the NTS because of increased stretch. NTS neurons send excitatory signals to the caudal ventrolateral medulla (CVLM), which in turn sends inhibitory signals (GABAergic) to the RVLM. The RVLM is the primary
regulator of the sympathetic nervous system (SNS) sending excitatory (glutamatergic) signals to the sympathetic preganglionic neurons located in the intermediolateral nucleus of the spinal cord. By inhibiting sympathetic activity, TPR and cardiac contractility is reduced, while parasympathetic nervous system (PNS) output via the vagus nerve is unaffected decreasing HR (LaRovere et al., 2008), Q and BP. Conversely, when the baroreceptors sense a decrease in BP, firing is less frequent from the baroreceptors thus SNS activation increases TPR, HR and cardiac contractility, thereby increasing Q and BP (Purves and Williams, 2001).

The HR response to PNS/vagal activity occurs more rapidly than that of SNS activity and as such has predominant control over the cardiovagal baroreflex loop. The parasympathetic nerves innervating the heart originate within the NTS which synapse with parasympathetic preganglionic neurons of the nucleus ambiguus. Cholinergic neurons travel to the cardiac neurons via vagus nerve branches. These branches terminate at the sinoatrial (SA) and atrioventricular (AV) nodes of the heart. The parasympathetic neurotransmitter acetylcholine binds directly to nicotinic receptors, causing a quick response via molecules located mostly within the cell membrane. Acetylcholine is removed by acetylcholinesterase within the synaptic cleft, or taken up into the presynaptic cleft almost instantly (Gordan et al., 2015). It has been found that PNS activity begins to respond to increases in BP within 200-600 ms reaching its peak effect at 0.5 seconds, with a return to baseline by 1 second. The PNS is therefore able to decrease HR within one cardiac cycle. Hence, when BP rises, the PNS responds by depressing HR thus lowering Q (Gordan et al., 2015)
Sympathetic output responds to decreases in BP within 2-3 seconds and has a maximum effect at 4 seconds and returns to baseline within 20 seconds of baroreceptor deactivation (LaRovere, 2008). For the sympathetic neurotransmitter norepinephrine to bind to muscarinic receptors and exert its effects, secondary messenger activation is required in the cytosol, causing a time delay in sympathetic activation (LaRovere, 2008), thus causing a delayed increase in BP. As well, neuronal norepinephrine removal is by way of reuptake into the presynaptic neuron. The duration of norepinephrine released by the adrenal gland is significantly longer than neuronally released norepinephrine. Consequently, the duration of its effects are longer. Blood-borne norepinephrine must travel to the liver to be deactivated. This clearance is a much more prolonged process, therefore the effects of blood-borne norepinephrine last up to 1-2 minutes, as opposed to neural catecholamines which only lasts for seconds (McCorry, 2007).

2.4.2 Cardiovagal Baroreflex Sensitivity

Cardiovagal baroreflex sensitivity (cvBRS) is an overall measure used to quantify the efficacy of the baroreceptor reflex to buffer changes in BP through changes in HR. More specifically, cvBRS is defined as a change in HR (bpm), or RR-interval (RRI; ms) per unit change in BP (mmHg). Normal cvBRS values range between 3-34 ms/mmHg (Tank et al., 2001). Reduced cvBRS is associated with CVD and death in individuals following myocardial infarction (Eckberg et al., 1997). A cvBRS lower than 3 ms/mmHg is considered to be clinically indicative of CVD (La Rovere et al., 1998). Therefore, cvBRS is a clinically relevant measure of current and future cardiovascular health.

It is well established that measures of cvBRS tend to be depressed in HTN (Gribbin et al., 1971; Palatini & Julius, 2009). However, changes in BP have not been
found to be a direct contributor to decreased measures of cvBRS. Changes in cvBRS in response to HTN are thought to be mediated by changes in arterial stiffness as the arteries shift to favour a less distensible but durable formation, thus decreasing the stretch of the arteries and afferent flow from the baroreceptors (Chesterton et al., 2005). As well, changes in central nervous system mechanisms have also been proposed to contribute to decreased cvBRS in HTN (Heesch, 1999).

Baroreceptors maintain BP around a homeostatic or set-point bringing BP back to this value when acute perturbations in BP occur (Monahan, 2007). Any change in pressure modifies baroreceptor discharge and through modifications in the autonomic output, returns BP to the set-point value. However, in the case of HTN when BP is elevated for a prolonged period, the activity-pressure relationship resets to a higher pressure (see Figure 1). This resetting occurs along with a reduction in baroreceptor sensitivity (Chapleau et al., 1988). While baroreceptor resetting does not counter sustained HTN, it does preserve the function of the baroreceptor system and maintains the ability to buffer acute changes in arterial BP at the new higher set-point (Kunze, 1985). This means that the same pressure value can be associated with different discharge patterns depending on the long-term BP level, which implies that there is no definite relationship between MAP and baroreceptor activity. This suggests that the baroreceptor pathway is not involved in the long-term regulation of BP (Krieger, 1988). However, there is a current shift in paradigm of baroreceptor-mediated BP regulation as recent findings by Lohmeier and colleagues and others suggest that arterial baroreceptors are involved in the long-term regulation of BP (Lohmeier and Iliescu, 2015; Kougias et al., 2010).
Figure 1: Baroreceptor resetting in hypertension (Adapted from Heesch, 1999)
MAP= mean arterial pressure, mmHg= millimetres of mercury, - - - = hypertension, — = normotension

2.4.3 Methods of Measuring Cardiovagal Baroreflex Sensitivity

Traditionally, cvBRS has been assessed during the application of stimuli that alters BP. Such methods include pharmacological methods, the Valsalva maneuver and neck suction. More recently cvBRS analysis has been estimated using spontaneous methods.

2.4.3.1 Pharmacological Methods

Pharmacological methods of cvBRS measurement utilize a pressor agent which raises or depresses BP. The resultant change in BP stimulates the baroreceptors accordingly and changes RRI to reestablish a homeostatic BP. As a result, changes in
SBP are regressed against changes in RRI and the coefficient results provide an estimate of cvBRS in ms/mmHg. One common method of pharmacological cvBRS quantification involves the injection of a graded bolus of phenylephrine, a vasoconstrictor drug to increase SBP between 15 and 40 mmHg. It is assumed that since the vagal response is rapid, the linear relationship between RRI and SBP reflects cvBRS. The resultant slope of the regression of change in RRI to change in SBP is expressed as ms/mmHg. It is also possible to measure cvBRS using a vasodilatory drug (i.e. amyl nitrite), and measure the acceleration of RRI (Parmer, 1992).

One advantage of this method is that it does not require participant cooperation or the need for a participant to exert any physical force, such as with the Valsalva maneuver (LaRovere, 2008). However, it is limited by the lack of specificity as this type of stimulus also activates the cardiopulmonary receptors. As well, the pressor agent phenylephrine initiates a reflex cardiac response (Milic, 2009). Additionally, pharmacological methods are invasive.

### 2.4.3.2 Valsalva Maneuver

The Valsalva maneuver involves a forced expiration against a closed airway or obstruction. A forced expiration of 40 mmHg for 15-20 seconds causes an initial decrease, then an increase in BP with a corresponding tachycardic then bradycardic response due to baroreceptor activation (Porth et al., 1984). The Valsalva maneuver can be performed in the seated or supine position and is typically repeated 3 times separated by 5-minute intervals while beat-by-beat BP and RRI are measured (Singer et al., 2001). These measurements are subject to linear regression analysis to estimate cvBRS. cvBRS estimates provided by the Valsalva maneuver are limited by the fact that the alterations in
pressure also trigger chemoreceptors, cardiopulmonary receptors, and induce changes in respiratory muscle tone (La Rovere, 2008). Additionally, this method requires a certain level of participant compliance to properly perform.

### 2.4.3.3 Neck Chamber

The neck chamber method examines cvBRS of the carotid baroreceptors. This technique is based on the theory that afferent baroreceptors can be stimulated by increasing or decreasing pressure surrounding the artery (Ludbrook et al., 1977). A chamber is placed around the neck and air pressure is applied or withdrawn within the chamber to apply changes in transmural pressure to the artery studied. The pressure changes lead to carotid baroreceptor activation or deactivation. Using this method cvBRS can be calculated as the slope of the regression between the neck suction or pressure applied and the corresponding RRI response (LaRovere et al., 2008). This method is limited by the fact that it only examines carotid baroreceptor function which is counteracted by the aortic baroreceptor function in response to the change in BP (Cooper & Hainsworth 2009). This method can also be uncomfortable for the participant as only 60-80% of pressure applied to the skin is transmitted to the artery (Ludbrook et al., 1977).

### 2.4.3.4 Spontaneous Methods

While traditional methods of cvBRS estimation are still used, technological advancement has allowed for cvBRS to be quantified non-invasively during resting conditions. Spontaneous methods of cvBRS assessment include sequence analysis (time domain) and spectral analysis (frequency domain). Time and frequency methods allow us to quantify naturally occurring beat-by-beat changes in RRI and BP (Frattola et al., 1997). This allows researchers to evaluate cvBRS without added devices or pharmacological
agents in a time and cost effective manner. Spontaneous methods of cvBRS analysis are more sensitive than pharmacological methods at detecting depressed cvBRS, for example in individuals with HTN (Milic, 2009).

The sequence method utilizes the time domain, identifying sequences where SBP and RRI increase or decrease simultaneously. The analysis of these intervals consist of 3 or more consecutive beats in which both SBP and RRI simultaneously rise or fall (Parati et al., 1988). The average slope of changes in SBP and RRI can be taken as an index of cvBRS. This method however only uses some of the data since only increasing and decreasing sequences are used (Hughson et al., 1993).

For this study population spontaneous methods of cvBRS analysis will be used, specifically the spectral method of cvBRS analysis. This method incorporates all data collected and is commonly used on large samples due to its reproducibility and high processing speed (Dias da Silva et al., 2009). The spectral method of cvBRS analysis has been demonstrated to be highly correlated with cvBRS measured using the phenylephrine method ($r=0.94$) (Milic, 2009).

Heart rate variability (HRV) is a measure of the oscillations in beat-to-beat HR or RRI intervals of a time series (Task Force, 1996). Similar to HRV, blood pressure variability (BPV) is a measure of the oscillations in beat-to-beat BP (Parati et al., 1995). HRV and BPV largely represent autonomic modulation of HR or BP, respectively. In the frequency domain, HRV and BPV are determined by performing power spectral density (PSD) analysis of a time-series. PSD analysis involves the decomposition of a time-series tachogram to sine waves of differing amplitudes and frequencies with the resultant sums of these sine waves generating power spectral peaks, revealing how power (variance) is
distributed as a function of frequency (Omboni et al., 1996). There are a number of peaks that exist in both HRV and BPV: high frequency (HF: 0.15 - 0.04 Hz), low frequency (LF: 0.04 - 0.15 Hz), very low (0.003 - 0.04 Hz) and ultraslow (<0.003 Hz) frequencies. Among HRV measurements, low frequency (LF) power is associated with both SNS and PNS activity (Billman, 2009; Malliani et al., 1991) and high frequency (HF) power is associated with respiratory and PNS alterations (Eckberg, 2003; Akselrod et al., 1985), while the LF to HF ratio represents sympathovagal balance (Eckberg, 1997).

From spectral analysis, cvBRS uses the gain or modulus of the transfer function between variations in SBP and RRI in the LF band (Robbe, 1987). The LF band has been shown to demonstrate changes in vasomotor tone, and is indicative of both parasympathetic and sympathetic modulation of RRI (Pomeranz et al., 1985; Saul, 1991). Hence, by determining the relationship between RRI and SBP in the LF band, cvBRS can be estimated (Saul et al. 1991; Head et al., 2001; Task Force, 1996).

2.4.4 Significance of Cardiovagal Baroreflex Sensitivity

Alterations in HRV, BPV and cvBRS have been associated with numerous negative health outcomes, such as cardiovascular morbidity and mortality and poor prognosis once a cardiovascular event has occurred. For example, the ATRAMI study (Autonomic Reflexes after Myocardial Infarction) found that low HRV and cvBRS are associated with sudden cardiac death, cardiac mortality and increased occurrence of arrhythmias after myocardial infarction (LaRovere et al., 1998). BPV has been demonstrated to correlate with organ damage, organ damage progression, and cardiovascular morbidity (Sega et al., 2002). In addition, HRV and cvBRS are often reduced during congestive heart failure due to sympathetic activation and this reduction
of HRV and cvBRS negatively impacts prognosis (Roche et al., 2001). Decreases in cvBRS in the development of HTN (Carthy, 2014), coronary artery disease (Katsube, 1996), obesity (Skrapari et al., 2007), hypercholesterolemia (Koskinen et al., 1995), diabetes (Lindgren et al., 2006), physical inactivity (Monahan et al., 2000) as well as the aging process (Laitinen, 1998) have also been found.

In particular, autonomic dysfunction has been demonstrated early in the development of HTN (Carthy, 2014). This presents as decreased HRV and increased BPV (Carthy, 2014; Zhang et al., 2012). Autonomic dysfunction is characterized by vagal withdrawal, sympathetic over-activation and increased Q (Carthy, 2014). Hence, cvBRS has been observed to decrease with increased BP levels (Bristow et al., 1969; Eguchi et al., 2007). Other measures of autonomic function have shown a shift towards sympathetic predominance, such as muscle sympathetic nerve activity (MSNA) and plasma catecholamine levels have also been linked with HTN (Carthy, 2014).

Arterial stiffness has been implicated in decreasing cvBRS (Mattace-Raso et al., 2007). Arterial stiffness is related to cvBRS in that the baroreflex pathway is dependent on the distension of the baroreceptors, which are located within the carotid sinus and aortic arch. When arteries are stiff, they are less able to distend. Since baroreceptors in the carotid sinus and aortic arch depend on stretch as a stimulus, the magnitude of the stimulus is diminished, in turn decreasing the magnitude of the signal sent to the brain. The decrease in stretch causes decreased afferent firing and thereby an overall increase in sympathetic activity, causing increased BP. While a large change in BP may elicit a large response in an individual with distensible arteries, in an individual with stiff arteries, that stimulus is diminished (Okada et al., 2012).
2.5 **Arterial Stiffness**

Arteries are composed of 3 layers: tunica adventitia, tunica media and tunica intima. Tunica adventitia is the outermost layer and composed of connective tissue. The tunica media is the thickest layer and contains the external elastic membrane and lamina composed of smooth muscle cells and collagen. The media layer makes up the bulk of the arterial wall and determines the vessel’s mechanical properties by contracting or relaxing to change the diameter of the lumen regulating blood flow and pressure. The tunica intima is the innermost layer and is the thinnest layer composed of the internal elastic membrane and endothelial cells in contact with the lumen of the vessel (Kohn et al., 2015).

Arterial elasticity is a term that describes the mechanical property of arteries to deform in response to changes in BP and/or volume (Bramwell and Hill, 1922; Avolio, 2013). Arterial stiffness is the opposite of arterial elasticity and refers to the capacity of a vessel to maintain its shape and resist stretch (Laurent et al., 2006). Arteries have an inherent stiffness due to the composition of two proteins in the media of the arterial wall: collagen and elastin. Collagen is a protein responsible for tensile strength of an artery, whereas elastin is an extensible fibre. Arteries become stiffer when collagen increases and elastin decreases (Cavalcante et al., 2011). In fact, arterial stiffness varies throughout the body. The most elastic arteries are the central arteries, which accommodate the greatest pressures and volumes ejected from the heart. Arteries become stiffer more distally as the vasculature becomes less elastic and more muscular. Peripheral arteries contain more smooth muscle cells, collagen and less elastin. These vessels are less elastic and regulate the rate of blood flow to a given area (Mitchell, 2008). The peripheral
arteries withstand less stress than the central arteries, being exposed to less pressure change as pressure has been buffered by the more central elastic arteries (Humphrey et al., 2016).

Overall, the elasticity of arteries depends on the relative makeup of collagen and elastin in the arterial wall (Greenwald, 2002). Decreased elastin and increased collagen decreases arterial elasticity. For example, as individuals age elastin becomes fragmented, decreasing the elasticity of an artery (Lee and Oh, 2010). Therefore, in compensation for the decreased structural integrity of the elastin, the arterial wall lays down more collagen to maintain the structural integrity of the arterial wall (Kohn et al., 2015), thus shifting the arterial mechanical properties towards increased stiffness. In particular, changes in stiffness affect primarily the central arteries (aorta and carotid artery), while the peripheral vasculature is affected to a lesser degree (Zieman, Melenovsky, & Kass, 2005). In fact, there are a number of different methodologies that can be used to assess differences in arterial stiffness characteristics specific to vasculature location, as well as changes in arterial stiffness for a given artery.

2.5.1 Pulse Wave Velocity

Pulse wave velocity (PWV) is the speed that a pressure wave travels in the body between two locations. The gold standard method of measuring vascular stiffness is the carotid-femoral PWV (cfPWV) (Laurent et al., 2006). cfPWV reflects central arterial stiffness as it measures the time interval between the R-wave of the cardiac cycle, indicating ejection from the heart and the arrival of the pressure wave to the carotid and femoral artery at the proximal and distal sites respectively (Weber et al., 2009). In addition, common measurements of peripheral arterial stiffness include carotid-brachial
and carotid-radial for the upper body and femoral-toe and femoral-ankle for the lower body. PWV is indicative of arterial stiffness because BP waves travel faster in a stiffer artery, causing more turbulent flow. A slower PWV is associated with better arterial health (Stewart et al., 2003) as an elastic artery is able to absorb the pulsatile energy to a greater extent than a stiff artery. PWV is calculated as: \( \text{PWV} = \frac{\Delta D}{\Delta T} \), where \( \Delta D \) is the approximate distance (metres) between measurement sites and \( \Delta T \) represents the pulse wave transit time (PWTT) (seconds) (Mosti et al., 2000). One limitation regarding the measurement of PWV is that PWV travel distances are estimated by measuring surface distances on the body (Canepa et al., 2014). This becomes a significant problem when profound adiposity causes issues obtaining certain measures accurately, in addition to body shape changing the distances (Joly et al., 2009).

2.5.2 Arterial Distensibility

Arterial distensibility is a measure of local arterial elasticity. Distensibility is defined as the relative change in vessel diameter for a given change in arterial pressure. Changes in arterial diameter occur due to pressure waves exerting force against the arterial wall as blood is pumped through the vasculature (O’Rourke, 2002). It can be calculated as the difference between cross-sectional arterial area (\( \Delta \text{CSA} = \text{maximum CSA} - \text{minimum CSA} \)) divided by the product of pulse pressure (\( \text{PP} = \text{SBP} - \text{DBP} \)) and minimal cross-sectional area. The equation for this calculation is as follows:

\[
\text{Distensibility (mmHg}^{-1}) = \frac{\Delta \text{CSA}}{\text{PP} \times \text{CSA}_{\text{min}}}
\]

Distensibility is most commonly measured non-invasively using ultrasonography with a high-frequency linear array transducer, along with PP determined non-invasively by applanation tonometry. Measurement of distensibility is most commonly done in the
common carotid artery (CCA) 1-2 cm proximal to the carotid bifurcation due to its size, location and superficiality, which makes it easy to image (Figure 2). As well, CCA distensibility is indicative of aortic health (Nagai, 1999).

![Figure 2: Ultrasound image of the common carotid artery landmarks used for common carotid artery diameters](image)

### 2.5.3 Significance of Arterial Stiffness

Arterial stiffness is an independent predictor of CVD morbidity and mortality in patients with HTN (Laurent, 2005). PWV has been shown to be closely related to CVD risk factors such as obesity (Toto-Moukouo et al., 1986), fat distribution (Safar et al., 2006), HTN (Payne, 2010), diabetes (Prenner and Chirinos, 2015), hypercholesterolemia (Zieman, Melenovsky and Kass, 2005) and aging (Lee and Oh, 2010). In particular, the Framingham Heart Study found that for each standard deviation increase in cfPWV, CVD risk increased 48% (Mitchell et al., 2010).
Arterial walls naturally stiffen with age (Tanaka et al, 2000). Changes in the arterial wall with age are primarily driven by the fraying of elastin fibres due to the chronic exposure of pulsatile wall stress (Greenwald, 2007). Arterial stiffness affects the central and peripheral arteries differently. Central arteries are more subject to stiffening, while peripheral arteries are spared (Choi et al., 2010; McEniery et al., 2005). This difference is due to the relatively greater loads placed on the central arteries, which require greater elasticity to buffer changes in pressure.

In both HTN and aging, arteries are chronically exposed to mechanical stress and favour a more durable formation, increasing the proportion of collagen to elastin in the arterial wall (Payne et al., 2010). In HTN, this change is more pronounced, as the chronic stress placed on the wall is greater, eliciting greater changes (Franklin, 2005). As a result, individuals with HTN tend to have stiffer arteries to protect them from mechanical damage due to increased pressures. Arterial stiffness is the primary factor involved in increased systolic pressure in individuals of advanced age and with HTN (O’Rourke, 1990).

2.6 Exercise Training

Various forms of exercise training have been shown to have beneficial effects in preventing and treating HTN. Among individuals with HTN looking to decrease their BP and normotensive individuals looking to maintain their BP, ACC/AHA recommendations for physical activity include aerobic, dynamic resistance training and/or isometric resistance exercise (Whelton et al., 2017). Individuals are instructed to perform 90-150 minutes per week of aerobic exercise (AE) at 65-75% of heart rate reserve and/or dynamic resistance exercise (RE) for 90-150 minutes per week, 6 exercises 3 sets per
exercise for 10 repetitions at an intensity of 50-80% heart rate reserve or one-repetition maximum. More recently, isometric exercise, namely isometric handgrip (IHG) training has been introduced as part of the ACC/AHA and CHEP guidelines directing individuals to perform 4 2-minute contractions separated by 1-minute of rest at 30-40% of MVC for 3 sessions per week (Whelton et al., 2017; Leung et al., 2017).

AE has the largest body of evidence regarding its efficacy in lowering BP, however has poor adherence in non-research settings and is not effective in a subset of individuals (Kinoshita et al., 1988; Nami et al., 2000). As for dynamic RE, this type of training has gained popularity among HTN populations as it has been shown to offer a significant, though smaller decrease in BP, and can also increase muscular strength and endurance. While RE appears to be a promising intervention to decrease BP, it is currently an adjunct therapy alongside AE and more work on the appropriate training load is needed. In contrast, the parameters of IHG training are well-researched and has been demonstrated, in a recent analysis comparing AE, RE and IHG, to offer the greatest hypotensive benefit in the least amount of time (Cornelissen and Smart, 2013). AE, RE and IHG all have merit in their ability to decrease BP and improve cardiovascular health, earning them evidence category classifications of A (randomized controlled trials (overwhelming evidence); consistent pattern of findings with substantial studies), B (randomized controlled trials (limited data); few randomized trials exist which are small in size and results inconsistent) and C (non-randomized trials; observational studies (outcomes are from uncontrolled, nonrandomized and/or observational studies)) respectively from ACSM, indicating strong evidence for their efficacy in treating HTN.
The following section will outline current knowledge regarding AE, RE and IHG in the treatment of HTN.

2.6.1 Aerobic Exercise

AE works to decrease BP on both an acute and chronic scale. In 1981 Fitzgerald first observed post-exercise hypotension, a drop in BP following AE. Since then, this phenomenon has been demonstrated to be dose-dependent—the most intense exercise providing a greater decrease in BP compared to less strenuous exercise (Eicher et al., 2010). This relationship also depends on pre-exercise BP (Cornelissen and Smart 2013). Individuals with higher pre-exercise BP will experience a greater decrease in BP following exercise. Post-exercise hypotension has been observed in as little as 15 minutes of exercise at 40% VO\textsubscript{2} max (Kessler et al., 2012), which is highly clinically useful as individuals with HTN are unlikely to be able to perform long bouts of exercise (Guidry et al., 2006). Not only does AE produce acute decreases in BP, it can also decrease long-term BP where chronic AE produces larger changes in BP in those with HTN compared to normotensives. As such, HTN management guidelines typically include AE. For example, among individuals with resistant HTN a treadmill walking protocol of 3 times per week at slightly higher than aerobic threshold reduced 24-h BP by 6 (±12) mmHg SBP and 3 (±7) mmHg DBP over 8-12 weeks (Dimeo et al., 2012).

Findings linking AE to arterial stiffness have mixed results. Tanaka et al. (2000) observed a 25% increase in arterial compliance and a 20% reduction in β-stiffness after 3 months of AE in previously sedentary middle age to older men (53±2 years). However, in older patients with HTN the results are equivocal. A study by Petrella and Aizawa (2008) in individuals with medicated HTN (68.2±5.4 years) found that a training protocol at
70% VO\textsubscript{2} max over 20 weeks did not improve measures of arterial stiffness. However, an acute bout of maximal AE improved arterial compliance and \(\beta\)-stiffness, while lowering DBP and MAP (Petrella and Aizawa, 2008). A similar study in individuals with isolated systolic HTN (64±7 years) by Ferrier et al., (2001) demonstrated that 8 weeks of AE at 65% VO\textsubscript{2} max did not produce any changes in SBP, DBP or measures of arterial stiffness (cfPWV, CCA distensibility). Since only chronic studies with healthier participants have shown marked improvements in arterial stiffness, further work is needed to elucidate the relationship between arterial stiffness and BP in response AE training.

It has also been suggested that AE can decrease SNS over-activity typically seen in HTN. Laterza et al. (2007) demonstrated that among a population of patients with HTN performing three 60-minute AE sessions per week for 4 weeks at 70% VO\textsubscript{2} max, SBP, DBP, and MSNA decreased and cvBRS increased. By the end of the study, the patients with HTN were not significantly different from the normotensive controls. Even among individuals recovering from myocardial infarction, AE has been shown to improve cvBRS over non-trained individuals by more than 25% in as few as 4 weeks. Furthermore, among those who responded to the AE training, a 10-year follow-up demonstrated that these individuals had a significantly lower cardiac mortality (La Rovere et al., 2002). Therefore, AE has immediate and lasting effects on cvBRS in clinical populations.

Even though AE has obvious BP benefits in hypertensive populations, nearly 25% of individuals do not experience lower BP following AE (Hagberg et al., 2000). Individuals who do not experience post-exercise hypotension are also found to frequently not have a BP response to chronic AE (Liu et al., 2012). This finding suggests that
individuals who cannot benefit from AE may require other exercise modalities to manage their BP.

2.6.2 Resistance Exercise

Dynamic RE has been less explored compared to AE and therefore less commonly prescribed for BP management. However, resistance training is not contraindicated in most individuals with HTN by the Canadian Hypertension Education Program (CHEP) guidelines (2017) and is recommended by the ACC/AHA guidelines (2017). In addition to decreasing BP, RE has the added benefit of improving muscular strength and endurance (Pollock et al., 2000). Both of these are attributes post-menopausal women and the elderly struggle to maintain while these populations represent the bulk of hypertensive cases (Lima et al., 2012).

A RCT performed by Moraes et al. (2012) studied the effect of a 12-week RE program in individuals with un-medicated stage-1 HTN. The population was asked to discontinue antihypertensive medications for 4 weeks prior to the RE intervention. Traditional non-circuit RE was performed at 60% 1-repetition maximum (low to moderate intensity). The training protocol consisted of 3 non-consecutive one-hour RE sessions per week. Seven exercises were chosen (leg press, leg curl, chest press, lat pulldown, shoulder press, biceps curl and triceps extension) and 3 sets of 12 repetitions of each exercise were performed. This intervention produced a decrease of 16 mmHg SBP and 12 mmHg DBP. Changes in SBP were significant by week 2 of training and DBP by week 10.

Decreases in BP were also experienced by a population of elderly women with HTN performing a RE program. The RE program consisted of two weekly one-hour
sessions and was composed of stretching, treadmill walking and one set of 8-10 repetitions of six different resistance exercises (seated bench press, rotary cuff, leg extension, leg curl, leg press and front lat-pull down). Following 4 months of RE the women were able to lower their SBP by 14 mmHg and DBP by 4 mmHg compared to baseline. Other studies have found that the decreases in BP experienced following RE can be maintained for up to 14 weeks (Nasciemento et al., 2014). These findings are expanded upon by Miyachi in a 2013 meta-analysis which found that high-intensity RE increases arterial stiffness while moderate-intensity resistance training does not (Miyachi, 2013). Furthermore, it was stated that this relationship only exists in young individuals who have inherently lower arterial stiffness, since there was no change in arterial stiffness in middle-aged individuals. Additionally, the increases seen in measures of arterial stiffness although statistically significant were not clinically significant in these healthy populations.

In a 2008 RCT performed by Collier et al., a population of individuals with non-medicated pre-HTN and stage-1 HTN performed either 4 weeks of AE or RE to investigate the effects on arterial stiffness and BP. Both training modalities produced comparable decreases in SBP and DBP (-4.6 mmHg SBP, -3.1 mmHg DBP). The RE group experienced increases in peripheral and central PWV, while the AE group experienced a decrease in both these arterial stiffness measures. Since both groups demonstrated a similar reduction in BP, the authors suggest there may be different mechanisms acting to lower BP by each modality. Likewise, a 2007 RCT by Heffernan et al. compared the effects of RE and AE in individuals with pre-HTN population. It was found that while both groups experienced comparable decreases in BP, only the AE
group experienced improvements in both HRV and cvBRS, while the RE group experienced a decrease in both measures.

The idea that training modalities may lower BP through different pathways is interesting as nearly 25% of individuals do not experience a decrease in BP following AE training (Hagberg et al., 2000). However, no such study has directly targeted these individuals. Hence, individuals who do not respond to AE should be urged to try other exercise modalities such as RE or IHG to lower their BP.

2.6.3 Isometric Exercise

Isometric exercise is characterized by a sustained muscle contraction without a change in the length of the working muscle (Fleck & Kraemer, 2004). Humans however, are unable to perform pure static contractions, thus isometric contractions are classified as contractions involving minimal change in muscle length (Mitchell et al. 1974). Several modalities of isometric exercise have been studied, including both IHG and bilateral leg training to elicit decreases in BP. IHG has become a popular training modality as it has been shown to decrease BP in a short amount of time with minimal time commitment. IHG is contraindicated for individuals who have SBP between 160-180 and/or DBP 100-110 mmHg due to the possible acute increases in BP during IHG (McGowan et al., 2017). The 2017 CHEP guidelines mentioned IHG training as a viable BP-lowering option and IHG was included in the ACC/AHA guidelines (2017) as a valid exercise modality to decrease BP among those with, and aiming to prevent HTN. This section reviews what is known about isometric training including prescription and individual factors affecting the response to intervention. This section aims to summarize the methods and results of the
most relevant training studies performed. A summary of the relevant studies can be found in Table 1.

2.6.3.1 Training Protocol

The first study to examine the relationship between BP and isometric exercise was performed by Kiveloff & Huber in 1971. A population of 8 individuals with HTN performed 5-8 weeks of maximal whole-body isometric training for durations of 6 seconds at maximum voluntary contraction (MVC), 3 times daily. Kiveloff & Huber noted a decrease of 16-24 mmHg in SBP and 2-24 mmHg in DBP. This decrease was comparable to individuals receiving pharmacotherapy who noted a decrease of 4-28 mmHg and 2-14 mmHg in SBP and DBP, respectively. Among individuals who were on HTN pharmacotherapy and prescribed isometric training, baseline BP was maintained. However, working at maximum MVC is potentially dangerous due to the associated acute increase in BP during contraction.

The hypotensive response of isometric exercise was also noted in the workplace by Buck & Donner in 1985. Individuals with an occupation entailing greater isometric activity tended to have lower BP than individuals whose occupation required lower isometric activity. These results are difficult to interpret as occupational isometric activity was rated as a categorical variable. The nature of data collection made exposure to isometric activity difficult to quantify and did not specify individual differences in exposure to isometric activity. However, this discovery became the basis for many interventional studies.

The first interventional IHG training study to examine changes in BP was performed by Wiley et al. in 1992. A population of normotensive participants of a broad
age range (19-56 years) were recruited. Two protocols were tested to elicit a maximal hypotensive response. The first protocol consisted of 4 sets of 2-minute unilateral contractions performed at 30% MVC separated by 3 minutes of rest performed 3 days per week for 5 weeks. The second protocol consisted of 4 sets of 45-second unilateral contractions performed at 50% MVC 5 days per week for 5 weeks. In both cases participants had their BP measured at 5 weeks following the completion of their IHG intervention, followed by a 5-week detraining period. The first group noted a decrease of 13/15 mmHg, while the second noted a decrease of 10/9 mmHg. In addition, Wiley et al. found that after 5 weeks of detraining, BP values returned to baseline.

Badrov et al., (2013b) observed that training frequency affects the speed at which individuals achieve a hypotensive response to IHG training, but not the magnitude. A population of 35 young, normotensive women were selected for this study to train at 30% MVC. Among individuals training 5 times per week, a significant decrease in BP was observed at week 4. However, among individuals training 3 times per week, a significant decrease in BP was observed at week 8. The magnitude of this decrease in both groups was equal at 6 mmHg. No further changes in BP were noted among the 5 times per week training group in weeks 4-8. These findings indicate that there is a maximum hypotensive response reached regardless of training dosage, and the time to maximum effect is dependant on training frequency. However, these findings are not generalizable to the general population due to the notable absence of males in the study population. As Badrov et al., (2013b) found that training frequency affects the rate at which BP decreases, Carlson et al. (2016) also found that intensity plays a role. Forty individuals with HTN (35-65 years) were randomly assigned to either a 5% or a 30% MVC group.
Both groups performed 4, 2-minute unilateral IHG exercises separated by 3-minutes of rest 3 days per week. Both SBP and MAP were found to significantly decrease in the 30% MVC group, while no significant changes in BP were found in the 5% MVC group following 8 weeks of IHG training. Hence, this study shows that training intensity also has an impact on BP changes in response to an IHG training protocol.

To date much of the literature has focused on IHG training however, recently another isometric training protocol has been introduced, that of isometric leg exercise (ILE). Using a leg extension dynamometer, Somani et al. (2017) recruited 46 healthy, young normotensive individuals and had them perform 4 sets of 2-minute isometric contractions at 30 or 32% of IHG and ILE, respectively. The intervention lasted 10 weeks and the protocol was performed 3 times per week. It was found that both ILE and IHG elicited a similar decrease in BP following training.

Another ILE that has been shown to be relatively safe and in accordance to the ACSM guidelines for AE termination (Wiles et al., 2018) is the isometric wall squat, which rivals IHG for its convenience and can be performed at a much lower price point. In a study by Wiles et al., (2017), 28 normotensive young males were recruited to perform a crossover design study that consisted of a 4 week at-home isometric wall squat program and a 4-week washout period. For the exercise intervention, participants performed 4 sets of 2-minute bouts of isometric wall squat exercise 3 times per week. The intensity of the wall squat was prescribed based on a graded wall squat test where the knee joint angle that induced a target HR of 95% peak was chosen. This training program was successful in significantly reducing SBP, DBP and MAP, as well as CO and HR.
As been shown by the above studies, as well as two systematic reviews and meta-analysis publications by Carlson et al. (2014) and Inder et al. (2016), isometric exercise produces clinically meaningful reductions in BP. As well, factors within the training protocol that have been found to affect the magnitude of BP response include training intensity, duration and frequency. Moreover, individual level factors may also play a large role in BP response to a given training protocol such as age, baseline BP and prescription medications.

2.6.3.2 Individual Responses to IHG Training

Factors within the training protocol and modality have been demonstrated to affect the BP response to IHG training. However, there are also inter-individual factors that can affect this response. Some factors which have been demonstrated to predict the hypotensive response are baseline BP, pharmacological intervention, response to CV stressors, age and some research has even suggested that sex may play a role (Lawrence et al., 2015).

Firstly, resting BP upon beginning IHG training is a strong predictor of how effective IHG training will be to lower BP. In a multilevel analysis performed by Millar et al. (2007), it was found that among individuals with medicated HTN partaking in IHG training (8-10 weeks, 3x/week), the average decrease in SBP and DBP was 6 mmHg and 3 mmHg, respectively. It was noted that participants who entered the study with initially higher BP experienced the greatest reductions in BP. It was also found that reductions in SBP were lost in only 7-10 days following cessation of IHG training.

Another factor which may influence the magnitude of BP decreases in response to IHG training is whether or not participants are taking BP medications. To date, no study
has directly examined the effect of pharmacological intervention or specific drug classes on BP response to IHG training. It has been noted that the changes in BP we see in individuals with similar baseline BP are much greater among those who are not medicated compared to those who are medicated. For example, a study performed by Stiller-Moldovan et al. (2012) found that a smaller change in BP following 8 weeks of IHG training occurred compared to McGowan et al. (2006a) whose participants took fewer BP drugs, had higher SBP at baseline (134±4 mmHg vs 114±13 mmHg) despite IHG training being of comparable duration and frequency. In addition, many studies have enrolled individuals with well-controlled HTN and thus participants may not have had the same ability to decrease their BP as outlined by Millar et al. (2007). It could be hypothesized that since individuals who are taking more medications tend to have better BP control, they may have less potential to decrease their BP. Another hypothesis set forward is the potential for overlap between the effect of IHG and certain classes of BP medications (Stiller-Moldovan et al. 2012).

Other interventional strategies may also be able to identify IHG responders and non-responders. Millar et al., (2009) performed a study investigating whether a cold pressor test or serial subtraction task could predict the responsiveness to IHG training. The cold pressor test activates primarily the peripheral vascular alpha-adrenergic receptors causing a BP response. The serial subtraction test also causes increases in BP however; this is mainly due to beta-adrenergic receptor activation increasing Q and in turn a change in BP with a larger change in HR. As such, the cold pressor test causes a vascular response, whereas the serial subtraction test causes a myocardial response. It was found that among a population of 17 normotensive older individuals who had
completed an IHG training study 6 months prior, IHG training-induced decreases in BP were correlated with the serial subtraction task BP-induced response, but not that of the cold pressor test. This finding suggests that BP response to the serial subtraction task may be able to predict the ability of individuals to respond to IHG training. The study went on to explain that since increased BP reactivity during the serial subtraction task is primarily due to increased Q, as a result of increased activation of the beta-adrenergic system, and that the cold pressor test produces no such change. Therefore, it is less likely that IHG training induced changes in BP are caused by alpha-adrenergic mediated vascular modulations. In fact, the response to stressors has been shown to be relatively stable, controlled by genetics and underlying pathology, and thus may have clinical use in determining whether IHG training may be a suitable intervention to decrease BP. These findings are in agreement with Badrov et al. (2013a), who also found individual differences in the capacity to respond to IHG training. This team of researchers showed that SBP reactivity to serial subtraction and IHG tasks (a single sustained 30% MVC for 2 minutes on the non-dominant hand) correlated with the magnitude of SBP response to IHG training. Similarly, a 2017 study by Somani et al. used a 2-minute isometric exercise test (either ILE or IHG) to predict which individuals had the greatest potential to lower their BP in response to isometric exercise training. Individuals whose BP increased the most acutely in response to isometric exercise had the largest decrease in BP following ILE or IHG training.

To date, there is only one study which has examined the effect of age on the response to IHG training. Millar et al., (2008) compared the effect of IHG training on resting BP between the 25th and 75th percentile. It was found that those in the 75th
percentile had a significantly greater decrease in BP compared to the 25th percentile. It is however well-known that BP tends to increase with age, and no commentary was included regarding whether the older cohort had greater baseline BP than their younger counterparts.

As for the effect of sex, among a population of 40 normotensive adults it was found that women experienced a larger decrease in SBP than males while undergoing a bilateral leg isometric contraction protocol. The study used electromyography to determine what contraction intensity corresponded to a training intensity 20-30% of electromyography peak and performed 4, 2-minute contractions 3 days a week for 3 weeks. The women experienced a decrease of 7 mmHg while the men experienced only a decrease of 2 mmHg SBP, despite having no differences in BP at baseline (Gill et al., 2015). This study was the first of its kind to identify sexual dimorphism in response to isometric training. In contrast, Badrov et al., (2016) found that 8 weeks of unilateral IHG improved local brachial arterial endothelium-mediated vasodilation (FMD) and BP equally among male and female participants. Similarly, Somani et al., (2017) investigated the possibility of a sexual dimorphism in the BP response to IHG training among young, normotensive individuals. There were no differences in the magnitude in decreases in SBP and DBP among both women and men performing a 10-week IHG or ILE exercise intervention.

In summary, there are several possible individual level factors which may predict how one may react to IHG training. However, whether IHG training, is more effective than AE or RE is still under debate.

2.6.3.3 Isometric Handgrip vs Aerobic Exercise vs Dynamic Resistance Exercise
Recently, three studies have looked into how IHG compares to traditional AE/RE protocols with mixed results. A meta-analysis performed by Cornelissen and Smart in 2013 comparing all exercise studies performed on both individuals with normotension and HTN found that IHG lowered both SBP and DBP by the greatest magnitude when compared to AE, RE and combined training. In contrast, a RCT performed by Pagonas et al. (2017), found that IHG training did not elicit the same hypotensive response as AE over 12 weeks in a hypertensive population. However, the findings of this study were contested by Smart et al. (2017) citing many methodological issues including important differences between the control and experimental groups. These differences included BP at baseline, a known confounder of BP response to IHG, differences in dropout rates between groups (25% dropout rate in the AE group vs 8% in the control group and 4% in the IHG group) and baseline exercise regime (number of self-reported exercise sessions per week).

While there has been no consensus reached on whether IHG is superior to AE for the treatment of HTN, it is well-established that IHG is an effective adjunct method to control BP. This was shown in a recent study by Baross et al. (2017) who examined the effect of simultaneously performing AE and IHG. Forty-eight healthy sedentary participants (age 20.7±1.7 years) composed of 26 males and 22 females with normotensive BP were recruited. Participants were randomly allocated to either perform AE, IHG or combined AE+IHG for 6 weeks. Training was performed 4 times per week. The AE group performed 30 minutes of treadmill walking, the IHG group performed 3 sets of 10 second IHG at 20% MVC and the AE+IHG group performed the two interventions simultaneously. It was found that change in SBP in the AE+IHG group (-10
± 3 mmHg) was greater than that elicited by the AE or IHG alone. This study presents an interesting option for individuals who cite time as their barrier to exercise, and may present an option to maximize the change in SBP elicited by training.

IHG has been demonstrated to effectively decrease BP among normotensive, hypertensive and medicated hypertensive populations (Somani et al., 2017; Peters et al., 2005; Millar et al., 2013). However, little is known about how long the beneficial effects of IHG last post-intervention. To date, no study has investigated in detail the minimum frequency of training necessary to maintain improvements in BP. Additionally, there is no consensus regarding the mechanism underlying these beneficial effects, though many theories have been put forward.
<table>
<thead>
<tr>
<th>Primary Author</th>
<th>Year</th>
<th>Population</th>
<th>Training Protocol</th>
<th>Duration</th>
<th>Significant Findings</th>
</tr>
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<tr>
<td>Wiley</td>
<td>1992</td>
<td>Normotensive&lt;br&gt;20-35 years&lt;br&gt;N=10</td>
<td>4, 45-sec bilateral IHG, 50% MVC, 5X/wk</td>
<td>5 weeks</td>
<td>↓ SBP 10 mmHg, ↓ DBP 9 mmHg</td>
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<td></td>
<td>Unmedicated pre-hypertensive&lt;br&gt;29-52 years&lt;br&gt;N=18</td>
<td>4, 2-min unilateral IHG, 30% MVC, 3X/wk</td>
<td>8 weeks</td>
<td>↓ SBP 13 mmHg, ↓ DBP 15 mmHg</td>
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<tr>
<td>Ray &amp; Carrasco</td>
<td>2000</td>
<td>Normotensive&lt;br&gt;19-35 years&lt;br&gt;N=16</td>
<td>4, 3-min unilateral IHG, 30% MVC, 4X/wk</td>
<td>5 weeks</td>
<td>↓ DBP 5 mmHg, No change in MSNA</td>
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<tr>
<td>Taylor</td>
<td>2003</td>
<td>75% medicated hypertensive, 25% unmedicated hypertensive&lt;br&gt;69±6 years&lt;br&gt;N=17</td>
<td>4, 2-min bilateral IHG, 30% MVC, 3X/wk</td>
<td>10 weeks</td>
<td>↓ SBP 19 mmHg, ↓ LF:HF HRV</td>
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<tr>
<td>Peters</td>
<td>2005</td>
<td>Unmedicated pre-hypertensive and hypertensive&lt;br&gt;52±5 years&lt;br&gt;N=10</td>
<td>4, 45-sec bilateral IHG, 50% MVC, 3X/wk</td>
<td>6 weeks</td>
<td>↓ SBP 13 mmHg, ↓ DBP 2 mmHg</td>
</tr>
<tr>
<td>McGowan</td>
<td>2006a</td>
<td>Medicated hypertensive&lt;br&gt;62±4 years&lt;br&gt;N=9</td>
<td>4, 2-min unilateral IHG, 30% MVC, 3X/wk</td>
<td>8 weeks</td>
<td>↑ brachial artery FMD, trained limb&lt;br&gt;↓ SBP 15 mmHg</td>
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<td></td>
<td>Medicated hypertensive&lt;br&gt;66±6 years&lt;br&gt;N=7</td>
<td>4, 2-min bilateral IHG, 30% MVC, 3X/wk</td>
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<td>↑ brachial artery FMD, both arms&lt;br&gt;↓ SBP 10 mmHg</td>
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Table 1: Literature review of IHG training studies examining changes in BP
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Group Description</th>
<th>Protocol Details</th>
<th>Duration</th>
<th>Changes/Outcomes</th>
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<td>67±6 years</td>
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<td></td>
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<td>N=7</td>
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<td></td>
<td></td>
<td>Acute ↓ brachial artery FMD</td>
</tr>
<tr>
<td>Millar</td>
<td>2007</td>
<td>Medicated hypertensives</td>
<td>4, 2-min unilateral or bilateral IHG, 30% MVC, 3X/wk</td>
<td>8 weeks</td>
<td>↓ SBP 5.7 mmHg, ↓ DBP 3 mmHg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>38-77 years</td>
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<td>N=43</td>
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<tr>
<td>McGowan</td>
<td>2007</td>
<td>Normotensive</td>
<td>4, 2-min unilateral IHG, 30% MVC, 3X/wk</td>
<td>8 weeks</td>
<td>↓ SBP 5 mmHg, ↔ brachial artery blood flow, ↔ brachial artery diameter</td>
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<tr>
<td></td>
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<td>28±14 years</td>
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<td></td>
<td>N=20</td>
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<tr>
<td>Millar</td>
<td>2008</td>
<td>Normotensive</td>
<td>4, 2-min bilateral 30-40% MVC performed on a spring handgrip trainer, 3X/wk</td>
<td>8 weeks</td>
<td>↑ SBP 10 mmHg, ↓ DBP 3 mmHg</td>
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<tr>
<td></td>
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<td>66±1 years</td>
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<td>N=56</td>
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<td>Devereux</td>
<td>2010</td>
<td>Normotensive males</td>
<td>4, 2-min bilateral ILE, 3X/wk, 95% HRpeak</td>
<td>4 weeks</td>
<td>↓ SBP 5 mmHg, ↓ DBP 3 mmHg, ↓ MAP 3 mmHg</td>
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<tr>
<td></td>
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<td>21±2</td>
<td></td>
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<td>N=13</td>
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<tr>
<td>Mortimer &amp;</td>
<td>2011</td>
<td>Normotensive females</td>
<td>4, 45-sec bilateral IHG, 30% MVC</td>
<td>5 days</td>
<td>↔ BP</td>
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<tr>
<td>McKune</td>
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<td>48±2 years</td>
<td></td>
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<td>N=18</td>
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<tr>
<td>Soares de</td>
<td>2011</td>
<td>Normotensive</td>
<td>4, 2-min bilateral IHG, 30% MVC</td>
<td>Acute</td>
<td>↑ SBP 16 mmHg, ↑ DBP 7 mmHg, ↑ HR 3 bpm</td>
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<tr>
<td>Araújo</td>
<td></td>
<td>64±9 years</td>
<td></td>
<td></td>
<td>SBP, DBP, HR return to baseline within 3 mins</td>
</tr>
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<td>N=41</td>
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<td>Stiller-</td>
<td>2012</td>
<td>Medicated hypertensive</td>
<td>4, 2-min bilateral IHG, 30% MVC</td>
<td>8 weeks</td>
<td>↔ Resting or ambulatory</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Type</td>
<td>Age ± SD</td>
<td>N</td>
<td>Intensity</td>
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<tr>
<td>Moldovan</td>
<td>2012</td>
<td>N=20</td>
<td>60±9 years</td>
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<td>MVC, 3X/wk</td>
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<td>Bartol</td>
<td>2012</td>
<td>N=20</td>
<td>70±5 years</td>
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<td>MVC, 3X/wk</td>
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<td>Badrov</td>
<td>2013a</td>
<td>N=12</td>
<td>23±4 years</td>
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<td>MVC, 3X/wk</td>
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<td>Badrov</td>
<td>2013b</td>
<td>N=24</td>
<td>65±6 years</td>
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<td>MVC, 5X/wk</td>
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<tr>
<td>Millar</td>
<td>2013</td>
<td>N=23</td>
<td>65±6 years</td>
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<td>MVC, 3X/wk</td>
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<td>Garg</td>
<td>2014</td>
<td>N=30</td>
<td>30±6 years</td>
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<td>MVC, 3X/wk</td>
</tr>
<tr>
<td>Gill</td>
<td>2015</td>
<td>N=30</td>
<td>23±3 years</td>
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<td>ILE, 3X/wk</td>
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<tr>
<td>Study</td>
<td>Year</td>
<td>Group Description</td>
<td>Protocol</td>
<td>Follow-up</td>
<td>Effects</td>
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<tr>
<td>Moon</td>
<td>2015</td>
<td>CAD patients, 63±9 years</td>
<td>3-min unilateral IHG, 30-40% MVC</td>
<td>Acute</td>
<td>↑ Central SBP, ↑ Central DBP, ↑ PWV</td>
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<td>Hess</td>
<td>2016</td>
<td>Normotensive, 39±11 years</td>
<td>4, 2-min unilateral IHG, 5% MVC, 3X/wk</td>
<td>6 weeks</td>
<td>↓ SBP 4 mmHg ↔ DBP</td>
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<td>4, 2-min unilateral IHG, 10% MVC, 3X/wk</td>
<td></td>
<td>↓ SBP 5 mmHg ↔ DBP</td>
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<td>Badrov</td>
<td>2016</td>
<td>Normotensive, Male 21±2 years, Female 23±4 years</td>
<td>4, 2-min unilateral IHG, 30% MVC, 3X/wk</td>
<td>8 weeks</td>
<td>↓ SBP 8 mmHg ↓ DBP 2 mmHg ↑ FMD equally in males and females</td>
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<td>Goessler</td>
<td>2016</td>
<td>Male CAD patients, 68±7 years</td>
<td>4, 2-min bilateral IHG, 30% MVC</td>
<td>Acute</td>
<td>↔ DBP, SBP, AMBP</td>
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<tr>
<td>Carlson</td>
<td>2016</td>
<td>Hypertensive, 65% medicated, 45% unmedicated, 52±8 years</td>
<td>4, 2-min unilateral IHG, 30% MVC, 3X/wk</td>
<td>8 weeks</td>
<td>↓ SBP 7 mmHg ↓ DBP 5 mmHg</td>
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<td>4, 2-min unilateral IHG, 5% MVC, 3X/wk</td>
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<td>↔ SBP, DBP</td>
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<tr>
<td>Baross</td>
<td>2017</td>
<td>Normotensive, 20±2 years</td>
<td>3, 10-second bilateral IHG, 20% MVC + 30-min walking 6.5 km/hr, 4X/wk</td>
<td>6 weeks</td>
<td>↑ SBP 10 mmHg, ↓ SBP 5 mmHg</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Group Description</td>
<td>Intervention Details</td>
<td>Duration</td>
<td>Blood Pressure Changes</td>
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<tr>
<td>Somani</td>
<td>2017</td>
<td>Normotensive 24±6 years N=46</td>
<td>20% MVC, 4X/wk 30-min walking 6.5 km/hr</td>
<td>6 weeks</td>
<td>↓ SBP 4 mmHg</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>4, 2-min bilateral IHG, 30% MVC, 3X/wk</td>
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<td></td>
<td></td>
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<td>4, 2-min bilateral ILE, 20% MVC, 3X/wk</td>
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<td>↓ SBP 7 mmHg</td>
</tr>
<tr>
<td>Wiles</td>
<td>2017</td>
<td>Normotensive males 30±7 years N=28</td>
<td>4, 2-min bilateral IHG, 30% MVC, 3X/wk</td>
<td>10 weeks</td>
<td>↓ SBP 4 mmHg</td>
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<td></td>
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<td>4, 2-min bilateral ILE, 20% MVC, 3X/wk</td>
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<tr>
<td>Goessler</td>
<td>2018</td>
<td>Normotensive adults 33±1 years N=60</td>
<td>4, 2-min bilateral IHG, 30% MVC, 7X/wk at home</td>
<td>8 weeks</td>
<td>↓ Daytime SBP 3 mmHg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4, 2-min bilateral IHG, 30% MVC, 7X/wk at home</td>
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<td>↓ Nighttime SBP 3 mmHg</td>
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<tr>
<td></td>
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<td>150 min moderate aerobic exercise total /wk at home</td>
<td></td>
<td>↓ Office SBP 4 mmHg</td>
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<td>↓ Office DBP 4 mmHg</td>
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<td>↔ Daytime or nighttime BP</td>
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<td></td>
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<td></td>
<td>↔ Office SBP 6 mmHg</td>
<td></td>
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<tr>
<td>Wiles</td>
<td>2018</td>
<td>Normotensive males 28±7 years N=20</td>
<td>4, 2-min 95% HRmax isometric wall squat, 2X/wk</td>
<td>2 weeks</td>
<td>BP stayed within ACSM</td>
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<tr>
<td></td>
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<td>safe range during</td>
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<td>isometric wall squat</td>
</tr>
</tbody>
</table>

N=number of participants, IHG=isometric handgrip training, SBP=systolic blood pressure, DBP=diastolic blood pressure, MAP=mean arterial pressure, MVC=maximum voluntary contraction, HR=heart rate, MSNA= muscle sympathetic nerve activity, PP=pulse pressure, PWV=pulse wave velocity, BP=blood pressure, LF=low frequency, HF=high frequency, HRV=heart rate variability, , FMD=flow mediated dilation, ILE=isometric leg extension, CAD=coronary artery disease, PEH=post-exercise hypotension, EMG=electromyography, week=wk, ACSM=American College of Sports Medicine
2.6.4 **Mechanisms of Blood Pressure Reduction**

To date, researchers have only hypothesized about the mechanisms eliciting physiological adaptations responsible for the decrease in BP associated with IHG training. Common theories include changes in autonomic function (HRV, cvBRS), enhanced vascular endothelial function, the inhibition of reactive oxygen species (ROS) and MSNA.

2.6.4.1 **Autonomic Function**

Changes in autonomic function have been suggested to occur with IHG training. However, studies that have investigated changes in autonomic activity following IHG training are equivocal. Most of the variance in these results have been attributed to differences in pharmacological BP regimes since certain classes of BP control medications target neural pathways involved in the HR reflex arm of the baroreflex, and theoretically may have already exerted the maximal change in autonomic adaptations (Stiller-Moldovan et al., 2012).

While the potential for improvement in autonomic function certainly exists in individuals with HTN, traditional measures of autonomic function such as HRV have not been shown to consistently improve with IHG training. Taylor et al. in 2003 aimed to determine whether decreases in BP seen in individuals with HTN (SBP >140 mmHg and/or DBP >85 mmHg, 75% medicated) following IHG were accompanied by an improvement in autonomic function. Participants performed 4 sets of 2-minute unilateral contractions at 30% MVC separated by 1-minute of rest 3 days per week for 10 weeks on a programmable handgrip dynamometer. It was found that SBP decreased by 19 mmHg and DBP decreased by 7 mmHg. It was also noted that there was a trend towards changes
in HRV, including LF:HF ratio and BPV, indicating an improvement in sympathetic to parasympathetic activity, hypothesized to contribute to the development of HTN. In contrast, Stiller-Moldovan and colleagues (2012) conducted a similar intervention among individuals with controlled HTN and found no change in HRV, but cited the fact that the participants’ BPs were well-controlled as a potential explanation for the lack of change in HRV. In 2013, Millar et al. found increased non-linear, but not traditional HRV indices in individuals with controlled HTN following an 8-week IHG intervention. The lack of conclusive evidence linking IHG training to improved autonomic function could be due to the above-mentioned studies using individuals with well-controlled HTN as their participants who may not have the potential to improve their autonomic function as individuals with higher BP. This idea is supported by Badrov et al., (2012a) who performed an IHG intervention on normotensive women, who also did not experience a change in autonomic activity as measured by HRV.

Changes in the baroreflex pathway, the primary mechanism controlling short-term changes BP, have not been investigated following IHG training. cvBRS is a method that has been recommended for study to potentially explain autonomic changes in response to IHG training (Badrov et al., 2013a).

2.6.4.2 Vascular Endothelial Function

Blood flow is reduced by occluding the flow to working muscles during IHG training with the degree of occlusion dependent upon the magnitude of the contraction (Barnes, 1979). When the contraction is released, blood is allowed to flow freely so that the shear force of blood flow on the arterial wall stimulates the release of nitric oxide (NO) from the endothelium. Shear stress up-regulates NO synthase, which increases the
release of endothelium-derived NO (Stewart et al., 2007). NO is a vasodilator which can reduce arterial BP and stiffness acutely, resulting in an acute hypotensive response.

Repeated exposure to shear stress is hypothesized to contribute to increasing basal NO bioavailability (Paniagua, Bryant and Panza, 2001). This is hypothesized to decrease BP chronically after a period of IHG training. This mechanism has been examined in both hypertensive and normotensive populations with varying results. NO mediated endothelial reactivity to shear stress can be evaluated through flow-mediated dilation (FMD). FMD involves inducing hyperemia by obstructing blood flow to the brachial artery, then upon release measuring the change in vessel diameter induced by shear stress and the corresponding NO-mediated vasodilation (Raitakari & Celermajer, 2000).

McGowan and colleagues (2006a) investigated the theory that BP reductions elicited by IHG training was caused by increased systemic endothelium-dependent vasodilation. A population of 16 individuals with medicated HTN individuals performed 4, 2-minute unilateral or bilateral IHG contractions at 30% MVC 3 times per week for 8 weeks. Brachial artery FMD improved in only the trained limb, in absence of any effect systemically. These findings suggest that among a medicated hypertensive population, increased systemic endothelium-dependent vasodilation is not the mechanism decreasing BP post-IHG intervention.

Another interventional study performed by McGowan et al. in (2006b) applied a unilateral training protocol consisting of 4 bouts of 2 minutes of IHG training separated by 1-minute of rest for 8 weeks among individuals medicated for HTN. Measures of endothelium-dependent (FMD) and endothelium-independent (nitroglycerin) vasodilation were taken pre- and post-training. Improvement in brachial endothelium-dependent
(FMD) function at rest post 8 weeks of IHG training was observed, while no change in endothelium-independent function was found. This suggests that BP reduction following IHG intervention is not driven by inherent changes in NO-dependent endothelial function.

The effect of IHG has also been investigated in normotensive individuals. In contrast to that observed in individuals with HTN, McGowan et al., (2007) observed no change in endothelium-dependent vasodilation following 8 weeks IHG training. Similarly, Badrov and colleagues (2013a) investigated the effects of IHG training frequency on both BP and resistance vessel endothelial function in normotensive women. They found that there were similar improvements in endothelial function and SBP among the groups training 3 or 5 times per week. However, both IHG training groups had decreased BP and increased forearm blood flow and improved resistance endothelial function compared to the control group. These findings were in the absence of changes in ANS function (HRV) and changes in DBP.

2.6.4.3 Reactive Oxygen Species

Peters et al., (2005) examined the potential role of reactive oxygen species (ROS) in mediating IHG-induced reductions in BP. They hypothesized that ischemia reperfusion caused by the release of isometric contraction increases antioxidant activity, neutralizing ROS thereby limiting damage to the blood vessels. It was hypothesized that the underlying mechanism by which oxidative stress may decrease BP is by the delivery of vasodilatory or obstruction of vasoconstrictive substances to the blood vessel wall. In this study a HTN population performed 4 sets of 45-second alternating unilateral IHG at 50% MVC separated by 1-minute rest 3 times per week for 6 weeks. Markers of antioxidants measured in this study included glutathione, ascorbic acid, and oxygen radical
absorbance capacity. Markers of ROS included oxidized glutathione and malonaldehyde. This population experienced a decrease in SBP of 13 mmHg and 2 mmHg DBP. Markers of oxidative stress were positively affected, with a decrease in total exercise-induced ROS (-266%), and an increase in resting whole blood oxidized glutathione (+61%), indicating increased antioxidant protection. These results suggest that IHG improves the ability of the blood vessel to clear vasoconstrictive substances and increases the circulating level of vasodilatory substances. The authors believe the attenuation of ROS provides a substantial contribution to the decrease in BP elicited by IHG training.

2.6.4.4 Sympathetic Nerve Activity

There is increasing evidence that HTN may be driven by sympathetic over-activation (Mancia & Grassi 2014). A study by Ray & Carrasco (2000) aimed to investigate whether changes in MSNA coincide with changes in BP seen with IHG training. Twenty-four normotensive individuals underwent either control, sham training or 4, 3-minute bouts of IHG exercise at 30% MVC separated by 5-minute rest periods 4 times per week for 5 weeks. Decreases in MAP and DBP were noted in the absence of changes in MSNA or SBP in the interventional group. These findings suggest that changes in BP elicited by IHG are not due to changes in MSNA. It was noted that the lack of change in MSNA may be attributed to the fact that the participants’ BPs were controlled and the response may appear only in individuals with HTN who demonstrated to have greater sympathetic activation.

While many theories have been tested with varying results, a definitive answer regarding which mechanism(s) are responsible for the decrease in BP elicited by IHG
training has not yet been found. Further research is required to explain the benefits of IHG interventions.

2.7 Statement of the Problem

Individuals with HTN struggle to control their BP due to poor adherence to exercise, medication and lifestyle modification interventions (Martin et al., 2005). Therefore, improving the ease of use and lowering the time commitment associated with IHG training may improve the long-term adherence and efficacy of this intervention to improve BP control and other CVD risk factors.

The primary questions that this study aimed to answer were: 1) What is the lowest frequency of training required to maintain initial improvements in BP following 8 weeks of traditional IHG training and 2) Is the BP response to IHG training in individuals with medicated HTN associated with concomitant increases in cvBRS and decreases in arterial stiffness indices.

It was hypothesized that: 1) Following IHG training 3 times per week for 8 weeks, BP reductions would be maintained with a minimum training frequency of 1 IHG session per week; 2) cvBRS would increase and arterial stiffness would decrease following IHG training 3 times per week for 8 weeks and would be further maintained with 1 IHG training session per week. If IHG can be performed in fewer sessions than traditionally prescribed either to decrease or maintain BP, long-term adherence to the training protocol for BP control could potentially be improved.
3 METHODOLOGY

3.1 Participants

Individuals with medicated HTN were recruited from the Brock-Niagara Centre for Health and Well-Being and Niagara region physician offices by posters, presentations at local venues and word-of-mouth over 24 months (October 2015 – September 2017). Interested individuals were invited to an initial visit by phone or email at either the Brock Niagara Centre for Health and Well- or the Human Hemodynamics Lab at Brock University.

Inclusion criteria involved taking one or more anti-HTN medications. Participants were excluded if they had been hospitalized within 3 months of baseline testing, had a change in medication within the prior 2 months and/or any physical limitation preventing them from performing IHG exercise. Individuals were allocated to each group based on order of enrolment.

The study aimed to recruit a sample size of 8 participants per group for a total of 24 participants. Sample size estimations and power calculations were performed using cvBRS data from previous data collected from the Human Hemodynamics Laboratory and reliability calculations from Gasch et al., (2011). It was determined that 8 participants per group is an adequate sample size as study power is 0.84. The effect size of this population is 3.41. However, the study population recruited totaled 16 participants.
Table 2: Sample size and power calculations based on cvBRS

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</tr>
<tr>
<td></td>
<td></td>
<td>0.159</td>
</tr>
<tr>
<td>Reject H₀</td>
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</table>

cvBRS=cardiovagal baroreflex sensitivity, H₀=null hypothesis

3.2 Study Design

This study received approval from the Brock University Biosciences Research Ethics Board (BREB, #15-065). Participants were placed into 1 of 3 training groups based on order of enrollment (See Figure 3).

- Group 1 performed 12 weeks of 3X/week IHG training (IHG3+3)
- Group 2 performed 8 weeks of 3X/week IHG training + 4 weeks of no IHG training (IHG3+0)
- Group 3 performed 8 weeks of 3X/week IHG training + 4 weeks of 1X/week IHG training (IHG3+1)
**Figure 3:** Overview of study design

BP=blood pressure, RRI=R-R interval, CCA=common carotid artery, PP=pulse pressure, wk=week, IHG=isometric handgrip training, IHG3+3=participants trained 3 times per week for 8 weeks then 3 times per week for 4 weeks, IHG3+0=participants trained 3 times per week for 8 weeks then 0 times per week for 4 weeks, IHG3+1=participants trained 3 times per week for 8 weeks then once a week for 4 weeks
Visit 1 consisted of informing the participant of study procedures and providing them with both an information letter (Appendix A), a full explanation of laboratory and training procedures, informed consent document (Appendix B), the ParMed-X and Health Care Provider (HCP) forms and, medical history form (Appendix C). Once the consent document was signed the researcher used an automated oscillometric BP monitor to measure seated resting BP. Automated BP measurements were taken using an automated brachial oscillometric device (Omron Healthcare, HEM-780 CANN, Illinois, USA). Participants were placed in the seated position with legs uncrossed, feet flat on the floor, and the non-dominant arm supported at heart level (Whelton et al., 2017). Four BP measurements were taken following 10 minutes of quiet rest, 2 minutes apart. The average of the closest 3 measurements were then averaged.

Visit 2 was then scheduled. During visit 2 the participants returned the HCP form as well as the completed ParMed-X. Automated BP measurements were taken and the participant was offered the opportunity to try the Zona handgrip protocol. Individuals were invited to perform two MVCs and two 2-minute isometric contractions at 30% MVC separated by a 1-minute rest. Lastly, the first laboratory testing session was scheduled.

All testing sessions were performed in the Human Hemodynamics Laboratory (Brock University). Participants were advised to continue with their prescribed medication regime throughout the study. Prior to each testing session, participants were asked to refrain from consuming caffeine and exercising for 24 hours. As well, testing was performed a minimum of 4 hours postprandial. Upon arrival to the laboratory, participants were asked to void their bladders prior to being outfitted with testing
equipment, as bladder distention is known to increase BP (Fagius et al., 1989). Participants were asked to sit quietly for 10 minutes, following which 4 seated BP measurements were taken using an automatic oscillometric BP device (Omron Healthcare, HEM-780 CANN, Illinois, USA). Anthropometric data, including standing height, body mass, waist and hip circumference were then collected. Following seated BP and anthropometric measurement, participants then rested supine on a table. Participants were fitted with standard ECG to collect beat-by-beat RRI. A finger cuff (Nexfin, BMEYE, Amsterdam, Netherlands) was placed on the left middle phalange to collect beat-by-beat BP. A pulse oximeter was placed on the left second toe. Three manual BP measurements were taken in the supine position by the auscultation method at the brachial artery following 10 minutes of rest. Following manual BP measurement, 10 minutes of continuous beat-by-beat RRI and BP data were collected. Carotid ultrasonography immediately followed on the right CCA. Local PP was taken at the left CCA and right radial artery for a minimum of 15 beats for the calculation of PWV. For an overview of the laboratory testing protocol refer to Figure 5. Identical testing procedures occurred at weeks 0 (pre-testing), 8 (midpoint testing) and 12 (post-testing) of the study. Following laboratory testing, two meetings per week with the researcher were scheduled to measure automated BP and perform IHG exercise.
Figure 4: Overview of laboratory testing protocol
BP=blood pressure, RRI=R-R interval, CCA=common carotid artery
Exercise training sessions were performed in the presence of a researcher on 2
days per week and the third session was performed at home. On the 2 days per week the
participants met with the researcher, the meeting began with 5 minutes seated rest, 4
measures of automated BP and then the IHG training protocol described in section 3.1.1
and recorded in a log book. The third session of the week was performed independently
and recorded by the participant in the logbook.

Following the initial 8 weeks, participants were placed into one of three training
groups based on order of enrollment. Participants were directed to either perform the 3
training sessions as described above, perform one day of training in the presence of the
researcher or abstain from IHG training. For all participants throughout the duration of
the 12 weeks of study, BP and HR were measured using an automated BP cuff twice per
week (Omron Healthcare, HEM-780 CANN, Illinois, USA). BP, arterial stiffness, cvBRS, and anthropometric data were collected at weeks 0, 8 and 12.

3.2.1 Isometric Handgrip Training Protocol

Participants performed unilateral MVCs on the right and then left hand. This was
followed by 2 sets of 2-minute unilateral isometric contractions performed alternating on
each hand at 30% of MVC, separated by a 1-minute rest. The training was performed
using a digital programmable handgrip dynamometer (Zona Plus, Zona Health Inc., Boise,
ID, USA), refer to Figure 4. The above protocol is endorsed by the ACC/AHA (2017)
and CHEP (2017). MVC was determined by performing one maximal contraction with
the right followed by the left hand using the handgrip trainer to measure the maximal
force produced by each hand prior to each training session. Two sessions per week were
performed under the supervision of the researcher and the third session of the week was performed by the participants at home after being given a detailed written description of how to properly conduct and record the results of the session (Appendix D). Supervised training sessions were recorded by the researcher and each participant was asked if they had any changes to medication, over-the-counter products or any major changes to diet or exercise regime in the past week in addition to being asked to provide verbal ongoing consent. Participants were also given a training log where they were to record the date of training, the MVC achieved by each hand, the percentage compliance to the protocol and any changes to their diet, physical activity, medication regime or any supplements during the days of unsupervised training (Appendix E). Following the initial 8 weeks of training, participants changed training frequencies to 0, 1, or maintaining 3 training sessions per week for 4 weeks.
Figure 5: IHG training protocol schematic

MVC = maximum voluntary contraction, R = right, L = left, IHG = isometric handgrip training
3.3 Measures

3.3.1 Anthropometry

Participants were assessed wearing light clothing and without shoes. Height (cm) was measured with a wall-mounted stadiometer (STAT 7X, Ellard Instrumentation Ltd., Monroe, WA, USA). Body mass was measured (kg) using an electronic medical scale (BWB-800S, Tanita Digital Scale, Tokyo, Japan). BMI (kg/m²) was calculated by dividing body mass by height squared. To calculate waist to hip ratio (WHR), waist circumference (cm) was measured around the narrowest point between the hips and ribs. Hip circumference (cm) was measured at the greatest gluteal protuberance (WHO, 2008). Each measure was repeated twice by the same researcher to ensure accuracy and decrease intra-observer variability and the average of the two measures were taken.

3.3.2 Cardiovascular Measurements

3.3.2.1 Blood Pressure and Heart Rate

BP was measured in 3 ways during testing for the proposed study: automated BP measurement, manual BP measurement and beat-by-beat BP. While automated BP measurement is similar to AOBPM and manual BP measurement is similar to OBPM, automated and manual BP measurements have some key differences between BP measurements taken in a clinical setting and a laboratory setting noted below.

Automated BP was taken during the intervention sessions using an automated brachial oscillometric device (Omron Healthcare, HEM-780 CANN, Illinois, USA). Participants were placed in the seated position with legs uncrossed, feet flat on the floor,
and the non-dominant arm supported at heart level (Whelton et al., 2017). Four BP measurements were taken following 10 minutes of quiet rest, 2 minutes apart. The average of the closest 3 measurements were then averaged.

Manual brachial BP was also taken using a standard mercury sphygmanometer. Manual BP measurements were taken in the supine position before and after beat-by-beat data collection. Manual BP measurements were used to adjust BP estimations from the finger and to assure that participants were at rest throughout data collection.

Beat-by-beat BP was measured using a photoplethysmography cuff (Nexfin, BMEYE, Amsterdam, Netherlands) attached to the left middle finger to collect SBP and DBP. Participants were also fitted with a standard single-lead electrocardiogram (ECG) to measure RRI. Sampling was at 1000 Hz, providing a resolution of 1 ms. Ten minutes of beat-by-beat data collection were collected in the supine position.

### 3.3.2.2 Baroreflex Sensitivity

Beat-by-beat RRI and BP data were collected at 1000 Hz using Powerlab and Chart 7 PRO (Version 7, ADInstruments Inc., Colorado Springs, CO, USA) and transferred into Microsoft Excel (2010). The most stable 5 minutes of data were used for cvBRS analysis. RRI sequences were visually inspected and any artefactual data was manually replaced with interpolated data. Using Matlab (MathWorks, 2012b), RRI and SBP were subjected to spectral and transfer function analysis as performed in previous studies in the Human Hemodynamics Laboratory (Chirico et al., 2015; Coverdale et al., 2012). Matlab (Mathworks, R2012b) software was used to resample the data using the mean cardiac frequency to obtain equal interval between samples. A Fast Fourier transform (FFT) was used for power spectral analysis (LF (0.04-0.15 Hz) and HF (0.15-
0.5 Hz) range) and mean transfer function gain was used to determine cvBRS for the LF region using a coherence of ≥0.5 (Chirico et al., 2015).

3.3.2.3 Common Carotid Artery Distensibility

A 5-beat series of 5 non-invasive imaging sequences of the right CCA was recorded using ultrasound (Vivid q, General Electric Medical Systems, Netherlands). Images were taken 1-2 cm proximal to the carotid bifurcation. Left CCA PP was measured non-invasively by applanation tonometry (Millar Instruments, Texas, USA) for 15 consistent beats. Ultrasound images were stored in Digital Imaging and Communications in Medicine (DICOM) format for later analysis. The two highest quality imaging sequences were used to determine diameter measurements. Diameter measurements were taken during systole and diastole. End-diastolic frames were taken at the time of the R-spike of the ECG recording and end-systolic frames at the time of the T-wave of the ECG recording. Three cardiac cycles for each of the 2 imaging sequences were selected, producing a total of 6 images. These images were stacked in a new DICOM file using commercially available software (Sante DICOM Editor, V. 3.1.24; Santesoft, Athens Greece). Images were then analyzed using semi-automated edge-tracking software (Artery Measurement System II, Image and Data Analysis; Gothenberg, Sweden) in regions of interest. Average pulsatile cross-sectional area (CSA) and the corresponding average CCA PP was used to determine vessel distensibility using the following equation:

\[
\text{Distensibility (mmHg}^{-1}) = \frac{\Delta \text{CSA}}{\text{PP} \times \text{CSA}_{\text{min}}}
\]
3.3.2.4 Pulse Wave Velocity

PWV was estimated using applanation tonometry. PP was collected using a handheld applanation tonometer (Millar Instruments, Texas, USA) that incorporates a high-fidelity strain gauge micro-manometer on the flattened end of a pencil-type probe. This probe was placed against the artery to allow the collection of arterial pressure waves. PP measurement was performed at the left carotid artery 1-2 cm proximal from the carotid bifurcation, and at the right radial artery. As well, a pulse oximeter (Nellcor N-200 Typco Healthcare Group LP, Pleasanton, CA, USA) was used to measure blood flow to the second left toe. Fifteen cardiac cycles of waveforms were collected. Distances from the sternal notch to each location were recorded to assure that measurements were taken in the same location in subsequent testing sessions as well as for determination of distances traveled to calculate velocities.

The foot of each pressure waveform was identified using a bandpass filter (5-30 Hz). Pulse wave transit time (T₂ and T₁) was then calculated relative to the R-wave of the ECG signal. The direct distances from the sternal notch to the carotid artery (D₁), radial artery or toe (D₂) were measured using an inelastic measuring tape over the body. PWV was calculated using the following formula:

\[
PWV = \frac{(D₂ - D₁)}{(T₂ - T₁)}, \text{ where } D \text{ is distance (metres) and } T \text{ is time (seconds)}.
\]

3.4 Statistical Analysis

Statistical analyses were performed using SPSS (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.). Significance level was set to \( \alpha \leq 0.05 \). Data are presented as mean ± SD for population, anthropometric and cardiovascular data. Shapiro-Wilk test for normality was used to test variables for
normality. Pre-testing group differences were evaluated using a chi-squared test for categorical variables and ANOVA for continuous variables.

Changes in cardiovascular function in response to exercise intervention between the 3 groups was evaluated using a mixed factorial ANOVA to determine a training effect for pre-, mid, and post-training. Significant differences were followed up with a Games-Howell post-hoc test to determine where the differences occurred. Changes in cardiovascular function over the first 8 weeks were analyzed with the data from all groups pooled using paired t-tests.

4 Results

Participants visited the lab twice per week for the duration of the training study and performed one training session at home independently, compliance with all training sessions was 100%. Furthermore, all training sessions were completed with greater than 90% accuracy. Participants were also asked to visit the laboratory for testing 3 times throughout the study (pre-, mid-, post-testing), laboratory sessions also had a compliance of 100%.

4.1 Baseline demographics

At baseline, no group differences were found for age, height, body mass, BMI or WHR. The medication regimes of the 3 groups were also not significantly different (Table 3).
Table 3: Subject demographics, anthropometry and medication history

<table>
<thead>
<tr>
<th></th>
<th>IHG3+3 (n = 5)</th>
<th>IHG3+0 (n = 4)</th>
<th>IHG3+1 (n = 7)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (%Female)</td>
<td>40%</td>
<td>50%</td>
<td>57%</td>
<td>0.869</td>
</tr>
<tr>
<td>Ethnicity (%White)</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>1.00</td>
</tr>
<tr>
<td>Age, years</td>
<td>63 ± 12</td>
<td>62 ± 7</td>
<td>69 ± 8</td>
<td>0.359</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.72 ± 0.12</td>
<td>1.66 ± 0.05</td>
<td>1.66 ± 0.05</td>
<td>0.308</td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>84.5 ± 21.3</td>
<td>82.7 ± 17.7</td>
<td>86.8 ± 10.5</td>
<td>0.974</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.9 ± 3.2</td>
<td>30.0 ± 6.4</td>
<td>32.1 ± 3.2</td>
<td>0.445</td>
</tr>
<tr>
<td>WHR</td>
<td>0.91 ± 0.07</td>
<td>0.97 ± 0.12</td>
<td>0.98 ± 0.04</td>
<td>0.352</td>
</tr>
</tbody>
</table>

Medication (n)

<table>
<thead>
<tr>
<th></th>
<th>IHG3+3</th>
<th>IHG3+0</th>
<th>IHG3+1</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-inhibitor</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0.807</td>
</tr>
<tr>
<td>Diuretic</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0.523</td>
</tr>
<tr>
<td>β-blocker</td>
<td>5</td>
<td>4</td>
<td>7</td>
<td>1.00</td>
</tr>
<tr>
<td>Ca2+ channel blocker</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>0.656</td>
</tr>
<tr>
<td>Angiotensin receptor blocker</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0.234</td>
</tr>
<tr>
<td>Alpha 2 receptor agonist</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0.234</td>
</tr>
<tr>
<td>Alpha 1 receptor agonist</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0.269</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.234</td>
</tr>
<tr>
<td>Statin</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>0.194</td>
</tr>
</tbody>
</table>

Values are means ±SD
BMI = Body mass index, WHR = waist to hip ratio, ACE = Angiotensin converting enzyme, Ca2+ = Calcium, n = number of participants, IHG3+3 = participants trained 3 times per week for 8 weeks then 3 times per week for 4 weeks, IHG3+0 = participants trained 3 times per week for 8 weeks then 0 times per week for 4 weeks, IHG3+1 = participants trained 3 times per week for 8 weeks then once a week for 4 weeks.
4.2 **Cardiovascular function**

Participants were not different for any measures of cardiovascular function at pre-testing (Table 4). Measures of cardiovascular function were measured over 8 weeks (pre-midpoint testing) as a grouped sample, as all participants performed identical training procedures (Table 5). Data were also measured in their individual training frequency groups at three timepoints. Data were examined over the initial 8-week training (pre-mid) and the final 4 weeks of training (mid-post).
Table 4: Subject baseline cardiovascular characteristics

<table>
<thead>
<tr>
<th></th>
<th>IHG3+3 (n = 5)</th>
<th>IHG3+0 (n = 4)</th>
<th>IHG3+1 (n = 7)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mmHg</td>
<td>133 ± 10</td>
<td>131 ± 13</td>
<td>134 ± 15</td>
<td>0.937</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>88 ± 9</td>
<td>80 ± 7</td>
<td>76 ± 7</td>
<td>0.080</td>
</tr>
<tr>
<td>PP, mmHg</td>
<td>45 ± 6</td>
<td>51 ± 11</td>
<td>58 ± 16</td>
<td>0.293</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>63 ± 11</td>
<td>65 ± 12</td>
<td>65 ± 11</td>
<td>0.627</td>
</tr>
<tr>
<td>cvBRS, ms/mmHg</td>
<td>9.75 ± 7.29 (n=4)</td>
<td>6.26 ± 3.25</td>
<td>8.24 ±4.31 (n=6)</td>
<td>0.390</td>
</tr>
<tr>
<td>LF-HRV, ms²</td>
<td>653.99 ± 480.28 (n=4)</td>
<td>232.00 ± 205.00</td>
<td>329.51 ± 212.43 (n=6)</td>
<td>0.388</td>
</tr>
<tr>
<td>HF-HRV, ms²</td>
<td>288.67 ± 171.0 (n=4)</td>
<td>99.79 ± 69.36</td>
<td>181.69 ± 181.85 (n=6)</td>
<td>0.577</td>
</tr>
<tr>
<td>LF/HF</td>
<td>2.03 ± 0.95 (n=4)</td>
<td>2.16 ± 0.36</td>
<td>2.65 ± 1.54 (n=6)</td>
<td>0.487</td>
</tr>
<tr>
<td>LF-BPV, mmHg²</td>
<td>14.00 ± 11.37 (n=4)</td>
<td>7.74 ± 5.14</td>
<td>4.87 ± 4.04 (n=6)</td>
<td>0.506</td>
</tr>
<tr>
<td>HF-BPV, mmHg²</td>
<td>2.26 ± 1.84 (n=4)</td>
<td>1.46 ± 0.89</td>
<td>2.94 ± 2.88 (n=6)</td>
<td>0.559</td>
</tr>
<tr>
<td>ctPWV, m/s</td>
<td>6.0 ± 1.6 (n=4)</td>
<td>7.2 ± 0.8</td>
<td>5.9 ± 0.7</td>
<td>0.153</td>
</tr>
<tr>
<td>crPWV, m/s</td>
<td>8.9 ± 0.7</td>
<td>9.0 ± 1.7</td>
<td>8.0 ± 1.1</td>
<td>0.568</td>
</tr>
<tr>
<td>CCA PP, mmHg</td>
<td>21 ± 10</td>
<td>21 ± 4</td>
<td>26 ± 6 (n=6)</td>
<td>0.359</td>
</tr>
<tr>
<td>Distensibility, mmHg⁻¹ x10³</td>
<td>5.5 ± 2.2</td>
<td>5.8 ± 1.6</td>
<td>4.3 ± 2.0 (n=6)</td>
<td>0.452</td>
</tr>
<tr>
<td>CCA LDmax, mm</td>
<td>7.2 ± 0.7</td>
<td>7.4 ± 0.5</td>
<td>7.7 ± 1.4 (n=6)</td>
<td>0.761</td>
</tr>
<tr>
<td>CCA LDmin, mm</td>
<td>6.8 ± 0.7</td>
<td>7.0 ± 0.6</td>
<td>7.3 ± 1.0 (n=6)</td>
<td>0.346</td>
</tr>
</tbody>
</table>

Values are means ±SD
SBP=seated brachial systolic blood pressure, DBP=seated brachial diastolic blood pressure PP=seated brachial pulse pressure, HR=seated heart rate, cvBRS=cardiovagal baroreflex sensitivity, LF=low-frequency, HF=high-frequency, HRV=heart rate variability, BPV=blood pressure variability, ctPWV=carotid-toe pulse wave velocity, crPWV=carotid-radial pulse wave velocity, CCA PP= supine common carotid artery pulse pressure, CCA=common carotid artery, LDmax=maximum lumen diameter, LDmin=minimum lumen diameter, n=number of participants, IHG3+3=participants trained 3 times per week for 8 weeks then 3 times per week for 4 weeks, IHG3+0=participants trained 3 times per week for 8 weeks then 0 times per week for 4 weeks, IHG3+1=participants trained 3 times per week for 8 weeks then once a week for 4 weeks.
### Table 5: Changes in cardiovascular characteristics following 8 weeks of IHG training

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Pre</th>
<th>Mid</th>
<th>Cohen’s d &amp; CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mmHg</td>
<td>16</td>
<td>133 ± 12</td>
<td>124 ± 15</td>
<td>0.64 (-0.09, 1.33)</td>
<td>0.004</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>16</td>
<td>81 ± 9</td>
<td>76 ± 9</td>
<td>0.53 (-0.19, 1.22)</td>
<td>0.006</td>
</tr>
<tr>
<td>PP, mmHg</td>
<td>16</td>
<td>52 ± 13</td>
<td>48 ± 12</td>
<td>0.32 (-0.38, 1.01)</td>
<td>0.085</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>16</td>
<td>64 ± 11</td>
<td>65 ± 10</td>
<td>0.10 (-0.60, 0.79)</td>
<td>0.889</td>
</tr>
<tr>
<td>cvBRS, ms/mmHg</td>
<td>14</td>
<td>8.11 ± 4.87</td>
<td>8.73 ± 4.51</td>
<td>0.13 (-0.62, 0.87)</td>
<td>0.386</td>
</tr>
<tr>
<td>LF-HRV, ms²</td>
<td>14</td>
<td>394.36 ± 333.28</td>
<td>650.72 ± 622.73</td>
<td>0.52 (-0.25, 1.25)</td>
<td>0.162</td>
</tr>
<tr>
<td>HF-HRV, ms²</td>
<td>14</td>
<td>188.86 ± 161.75</td>
<td>266.82 ± 254.06</td>
<td>0.36 (-0.39, 1.10)</td>
<td>0.832</td>
</tr>
<tr>
<td>LF/HF</td>
<td>14</td>
<td>2.33 ± 1.11</td>
<td>2.75 ± 1.50</td>
<td>0.32 (-0.44, 1.06)</td>
<td>0.165</td>
</tr>
<tr>
<td>LF-BPV, mmHg²</td>
<td>14</td>
<td>8.30 ± 7.60</td>
<td>9.43 ± 8.90</td>
<td>0.08 (-0.67, 0.82)</td>
<td>0.902</td>
</tr>
<tr>
<td>HF-BPV, mmHg²</td>
<td>14</td>
<td>1.93 ± 1.80</td>
<td>2.03 ± 1.50</td>
<td>0.06 (-0.68, 0.80)</td>
<td>0.389</td>
</tr>
<tr>
<td>ctPWV, m/s</td>
<td>15</td>
<td>6.2 ± 1.1</td>
<td>6.0 ± 1.0</td>
<td>0.26 (-0.47, 0.97)</td>
<td>0.069</td>
</tr>
<tr>
<td>crPWV, m/s</td>
<td>16</td>
<td>8.2 ± 1.7</td>
<td>7.7 ± 1.4</td>
<td>0.28 (-0.42, 0.97)</td>
<td>0.095</td>
</tr>
<tr>
<td>CCA PP, mmHg</td>
<td>15</td>
<td>24 ± 6</td>
<td>21 ± 5</td>
<td>0.48 (-0.26, 1.19)</td>
<td>0.194</td>
</tr>
<tr>
<td>Distensibility, mmHg⁻¹ x 10³</td>
<td>15</td>
<td>4.8 ± 1.8</td>
<td>4.2 ± 2.1</td>
<td>0.31 (-0.42, 1.02)</td>
<td>0.269</td>
</tr>
<tr>
<td>CCA LDmax, mm</td>
<td>15</td>
<td>7.4 ± 0.7</td>
<td>7.3 ± 0.7</td>
<td>0.20 (-0.52, 0.91)</td>
<td>0.146</td>
</tr>
<tr>
<td>CCA LDmin, mm</td>
<td>15</td>
<td>7.1 ± 0.9</td>
<td>6.9 ± 0.7</td>
<td>0.19 (-0.53, 0.91)</td>
<td>0.202</td>
</tr>
</tbody>
</table>

Values are means ±SD

SBP=seated brachial systolic blood pressure, DBP=seated brachial diastolic blood pressure, PP=seated brachial pulse pressure, HR=seated heart rate, cvBRS=cardiovagal baroreflex sensitivity, LF-HRV=low frequency heart rate variability, HF-HRV=high frequency heart rate variability, LF/HF=low frequency to high frequency heart rate variability ratio, LF-BPV=low frequency blood pressure variability, HF-BPV=high frequency blood pressure variability, ctPWV=carotid-toe pulse wave velocity, crPWV=carotid-radial pulse wave velocity, CCA PP=supine common carotid artery pulse pressure, CCA=common carotid artery, LDmax=maximum lumen diameter, LDmin=minimum lumen diameter, n=number of participants, Pre=pre-testing (week 0), Mid=midpoint testing (week 8), Cohen’s d=effect size, CI=confidence interval
4.2.1 **BP and HR**

BP was excluded for one participant at post-testing due to reported extreme emotional stress. This value was proven to be an outlier by Grubb’s test for outliers. Participant details for SBP, DBP, HR and PP are presented below in Table 6.
Table 6: Changes in basic cardiovascular characteristics following 8 and 12 weeks of IHG training

<table>
<thead>
<tr>
<th>SBP, mmHg</th>
<th>DBP, mmHg</th>
<th>PP, mmHg</th>
<th>HR, bpm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IHG3+3 (n=5)</td>
<td>IHG3+0 (n=4)</td>
<td>IHG3+1 (n=7)</td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>Mid</td>
<td>Post</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>133 ± 10</td>
<td>127 ± 13</td>
<td>125 ± 17 (n=4)</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>88 ± 9</td>
<td>82 ± 10</td>
<td>80 ± 13 (n=4)</td>
</tr>
<tr>
<td>PP, mmHg</td>
<td>45 ± 6</td>
<td>45 ± 8</td>
<td>45 ± 9 (n=4)</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>63 ± 11</td>
<td>65 ± 7</td>
<td>61 ± 8</td>
</tr>
</tbody>
</table>

Values are means ±SD
SBP=seated brachial systolic blood pressure, DBP=seated brachial diastolic blood pressure PP=seated brachial pulse pressure, HR=heart rate, n=number of participants, IHG3+3=participants trained 3 times per week for 8 weeks then 3 times per week for 4 weeks, IHG3+0=participants trained 3 times per week for 8 weeks then 0 times per week for 4 weeks, IHG3+1=participants trained 3 times per week for 8 weeks then once a week for 4 weeks; Pre=pre-testing (week 0), Mid=midpoint testing (week 8), Post=post-testing (week 12)
Among SBP data there was a significant main effect for time (p=0.036), but not for group (p=0.919) with no significant interaction (p=0.715). Post-hoc testing revealed that pre-testing SBP was significantly different from mid-point (p=0.015) and post-testing (p=0.047). When data from all 3 groups are pooled for the first 8 weeks, SBP decreased by 9±10 mmHg (p=0.004) (See Figure 6).
Figure 6: Changes in SBP following 8 and 12 weeks of IHG training
SBP=seated brachial systolic blood pressure, IHG3+3=participants trained 3 times per week for 8 weeks then 3 times per week for 4 weeks, IHG3+0=participants trained 3 times per week for 8 weeks then 0 times per week for 4 weeks, IHG3+1=participants trained 3 times per week for 8 weeks then once a week for 4 weeks, Pre=pre-testing (week 0), Mid=midpoint testing (week 8), Post=post-testing (week 12), * significant change from pre-testing
Among DBP data there was a trend towards a significant main effect for time (p=0.051) and group (p=0.064) with no significant interaction (p=0.526). When data from all 3 groups were pooled, DBP decreased by 5±6 mmHg (p=0.006) within the first 8 weeks (see Figure 7).

Figure 7: Changes in DBP following 8 and 12 weeks of IHG training
DBP=seated brachial diastolic blood pressure, IHG3+3=participants trained 3 times per week for 8 weeks then 3 times per week for 4 weeks, IHG3+0=participants trained 3 times per week for 8 weeks then 0 times per week for 4 weeks, IHG3+1=participants trained 3 times per week for 8 weeks then once a week for 4 weeks, Pre= pre-testing (week 0), Mid= midpoint testing (week 8), Post= post-testing (week 12), *significant change from pre-testing

There was no significant main effect for time (p=0.287) or group (p=0.134) on brachial PP with no interaction (p=0.723). Nor was there a significant change in HR with time (p=0.627) or group (p=0.881) with no interaction (p=0.932) across the 12 weeks of the study.
4.2.2 Indices of Autonomic function

Cardiovascular variables were measured for all individuals, however measures of HRV, BPV and cvBRS were not included in the analysis for two individuals; one in group IHG3+3 and one in group IHG3+1. For mid- and post-testing, one individual was not included due to reported extreme emotional stress, upon analysis these data were outliers upon Grubb’s test for outliers. For mid- and post-testing one participant reported upper respiratory illness causing the individual to cough excessively during the 10-minute collection period. Again these measures were not included as these values were found to be outliers by Grubb’s test for outliers and as such were not included at any timepoint. Participant details for measures of autonomic function at pre-, mid- and post-testing are presented in Table 7.

There were no statistically significant effects of time or group with no interaction among cvBRS (p=0.522; p=0.670; p=0.759), LF-HRV (p=0.252; p=0.531; p=0.579), HF-HRV (p=0.491; p=0.759; p=517), LF/HF ratio (p=0.184; p=0.825; p=0.593), LF-BPV (p=0.174; p=0.341; p=0.163), and HF-BPV (p=0.237; p=0.692; p=0.905) respectively. Additionally, when collapsing data across groups for the first 8 weeks of training, there were no statistically significant changes in the aforementioned variables.
Table 7: Changes in indices of autonomic function following 8 and 12 weeks of IHG training

<table>
<thead>
<tr>
<th></th>
<th>IHG3+3 (n=4)</th>
<th>IHG3+0 (n=4)</th>
<th>IHG3+1 (n=6)</th>
<th>Time</th>
<th>Group</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Mid</td>
<td>Post</td>
<td>Pre</td>
<td>Mid</td>
<td>Post</td>
</tr>
<tr>
<td>cvBRS, ms/mmHg</td>
<td>9.75 ± 7.29</td>
<td>10.19 ± 5.56</td>
<td>10.94 ± 5.92</td>
<td>6.26 ± 3.25</td>
<td>10.19 ± 5.56</td>
<td>8.32 ± 3.09</td>
</tr>
<tr>
<td>LF-HRV, ms²</td>
<td>653.99 ± 480.28</td>
<td>910.01 ± 1037.61</td>
<td>811.26 ± 876.06</td>
<td>232.00 ± 205.00</td>
<td>743.35 ± 539.54</td>
<td>220.54 ± 135.68</td>
</tr>
<tr>
<td>HF-HRV, ms²</td>
<td>288.67 ± 171.70</td>
<td>312.62 ± 286.86</td>
<td>241.02 ± 292.14</td>
<td>99.79 ± 69.36</td>
<td>352.63 ± 393.20</td>
<td>121.55 ± 85.00</td>
</tr>
<tr>
<td>LF/HF</td>
<td>2.03 ± 0.95</td>
<td>3.17 ± 2.49</td>
<td>3.37 ± 1.81</td>
<td>2.16 ± 0.36</td>
<td>2.98 ± 1.21</td>
<td>2.11 ± 1.20</td>
</tr>
<tr>
<td>LF-BPV, mmHg²</td>
<td>14.00 ± 11.37</td>
<td>13.60 ± 15.51</td>
<td>9.38 ± 11.42</td>
<td>7.74 ± 5.14</td>
<td>11.21 ± 6.42</td>
<td>2.84 ± 1.23</td>
</tr>
<tr>
<td>HF-BPV, mmHg²</td>
<td>2.26 ± 1.84</td>
<td>2.73 ± 1.70</td>
<td>1.54 ± 0.71</td>
<td>1.46 ± 0.89</td>
<td>9.47 ± 15.83</td>
<td>1.02 ± 0.561</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
cvBRS=cardiovagal baroreflex sensitivity, LF-HRV=low frequency heart rate variability, HF-HRV=high frequency heart rate variability, LF/HF=low frequency to high frequency heart rate variability ratio, LF-BPV=low frequency blood pressure variability, HF-BPV=high frequency blood pressure variability, n=number of participants, IHG3+3=participants trained 3 times per week for 8 weeks then 3 times per week for 4 weeks, IHG3+0=participants trained 3 times per week for 8 weeks then 0 times per week for 4 weeks, IHG3+1=participants trained 3 times per week for 8 weeks then once a week for 4 weeks, Pre=pre-testing (week 0), Mid=midpoint testing (week 8), Post=post-testing (week 12)
4.2.3 CCA Distensibility

For one individual in the IHG3+1 group CCA ultrasound measurements were made very difficult by participant non-compliance during testing. As such, their values were not included in the analysis for pre, mid- or post-testing. Participant details for arterial indices are presented below in Table 8.

For CCA PP there was no significant main effect for time (p=0.463) or group (p=0.343) with no interaction (p=0.148). CCA distensibility, LDmax or LDmin had no significant main effect for time (p=0.830; p=0.143; p=0.064) or group (p=0.464; p=0.693; p=0.579) with no interaction (p=0.850; p=0.202; p=0.187). When data for the first 8 weeks was pooled there was no significant change in CCA distensibility (p=0.269), carotid PP (p=0.194), LDmax (p=0.146) or LDmin (p=0.202).

4.2.4 Pulse Wave Velocity

For one individual in IHG3+3, ctPWV was not recorded at pre-testing due to equipment malfunction with the pulse oximeter and therefore was removed from analysis. PWV data at pre-, mid- and post-testing is presented in Table 6. For ctPWV there was a significant main effect of time (p=0.002) but not group (p=0.066) and an interaction was not found (p=0.512). Post-hoc testing revealed that there was a significant effect of time between pre- to post-testing (-1.2 ± 1.0, p=0.002) and mid- to post-testing (-0.8 ± 1.0, p=0.017). When ctPWV data was pooled there was no significant change in ctPWV (-0.37 ± 0.7 p=0.069) among the first 8 weeks of training.

Among measures of crPWV there was a significant effect of group (p=0.045) and time (p=0.030) without a significant interaction term (p=0.847). Post-hoc testing revealed
that there were no significant differences between groups, but it was revealed that there was a significant effect of time between pre- and post-testing (-1.4 ± 1.7 p=0.010). When examined as grouped data for the first 8 weeks of training decreases in crPWV were not significant (-0.68 ± 1.5, p=0.095).
Table 8: Changes in arterial indices following 8 and 12 weeks of IHG training

<table>
<thead>
<tr>
<th></th>
<th>IHG3+3</th>
<th></th>
<th></th>
<th>IHG3+0</th>
<th></th>
<th></th>
<th>IHG3+1</th>
<th>Time</th>
<th>Group</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n Pre</td>
<td>Mid</td>
<td>Post</td>
<td>n Pre</td>
<td>Mid</td>
<td>Post</td>
<td>n Pre</td>
<td>Mid</td>
<td>Post</td>
<td>p</td>
</tr>
<tr>
<td>CCA PP, mmHg</td>
<td>5</td>
<td>21 ±1 0</td>
<td>21 ± 5</td>
<td>4</td>
<td>21 ± 4</td>
<td>21 ± 3</td>
<td>6</td>
<td>26 ±6</td>
<td>19 ±6</td>
<td>0.463</td>
</tr>
<tr>
<td>Distensibility,</td>
<td>5</td>
<td>5.5 ±2.2</td>
<td>6.6 ±2.8</td>
<td>4</td>
<td>5.8 ±1.6</td>
<td>5.1 ±1.6</td>
<td>6</td>
<td>4.3 ±2.0</td>
<td>4.9 ±2.5</td>
<td>0.830</td>
</tr>
<tr>
<td>mmHg(^{-1})x10(^{-3})</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCA LDmax, mm</td>
<td>5</td>
<td>7.2 ±0.7</td>
<td>7.1 ±0.5</td>
<td>4</td>
<td>7.4 ±0.5</td>
<td>7.3 ±0.6</td>
<td>6</td>
<td>7.7 ±1.4</td>
<td>7.4 ±1.0</td>
<td>0.143</td>
</tr>
<tr>
<td>CCA LDmin, mm</td>
<td>5</td>
<td>6.8 ±0.7</td>
<td>6.7 ±0.5</td>
<td>4</td>
<td>7.0 ±0.6</td>
<td>7.0 ±0.6</td>
<td>6</td>
<td>7.3 ±1.0</td>
<td>7.0 ±0.9</td>
<td>0.064</td>
</tr>
<tr>
<td>ctPWV, m/s</td>
<td>4</td>
<td>6.0 ±1.6</td>
<td>6.0 ±1.0</td>
<td>5</td>
<td>5.5 ±0.5</td>
<td>6.9 ±1.0</td>
<td>7</td>
<td>5.9 ±0.7</td>
<td>5.5 ±0.8</td>
<td>0.002</td>
</tr>
<tr>
<td>crPWV, m/s</td>
<td>5</td>
<td>8.9 ±0.7</td>
<td>8.8 ±1.0</td>
<td>8</td>
<td>9.0 ±1.7</td>
<td>8.0 ±1.1</td>
<td>7</td>
<td>8.0 ±1.1</td>
<td>7.1 ±1.4</td>
<td>0.030</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
CCA PP= supping common carotid artery pulse pressure, LDmax=maximum lumen diameter, LDmin=minimum lumen diameter, ctPWV=carotid-toe pulse wave velocity, crPWV=carotid-radial pulse wave velocity, n=number of participants, IHG3+3=participants trained 3 times per week for 8 weeks then 3 times per week for 4 weeks, IHG3+0=participants trained 3 times per week for 8 weeks then 0 times per week for 4 weeks, IHG3+1=participants trained 3 times per week for 8 weeks then once a week for 4 weeks, Pre=pre-testing (week 0), Mid=midpoint testing (week 8), Post=post-testing (week 12)
5 Discussion

The aim of the present study was to determine if there were changes in cardiovascular variables following IHG training. These variables were measured over both an 8-week training period, and a subsequent 4-week period of 3 different training frequencies. Following the initial 8-week training regime, individuals who continued to train 3 times per week further decreased their BP over the subsequent 4 weeks of training. In contrast, individuals who trained once per week experienced a small increase in BP and individuals who stopped training experienced a larger increase in BP. This study both supports the existing literature about IHG training among individuals with medicated HTN and presents novel findings. The novel findings of this study were the significant reduction in both trained limb (crPWV) and systemic (ctPWV) measures of arterial stiffness over time. This study is the first of its kind to identify changes in systemic and regional arterial stiffness in response to IHG training.

5.1 Blood Pressure and Heart Rate

An overall significant decrease in SBP and a trend towards a decrease in DBP were found from pre- to mid- and pre- to post-testing, while a significant decrease in both SBP and DBP were found from pre- to mid-testing among all groups. No change in HR was identified in concordance with earlier work showing no changes in HR with IHG training (Millar et al., 2009; Taylor et al., 2003). Studies using an IHG intervention 8-10 weeks in duration have identified both statistically and clinically significant decreases in BP following IHG training in a medicated hypertensive population (Taylor et al., 2003;
McGowan et al., 2006a; Millar et al., 2007; Stiller-Moldovan et al., 2012; Millar et al., 2013; Badrov et al., 2013b; Carlson et al., 2016). It has been suggested in the literature that there are several individual factors that play a role such as age, degree of BP control and pharmacological intervention pathways (Lawrence et al., 2015). For example, it has been well-documented that individuals who begin IHG training with a higher BP stand to experience the largest decrease in BP (Millar et al., 2007). In reflection, our sample had varying degrees of BP control ranging from well-controlled to resistant HT, as well as a wide age range (50-76 years). These factors may help to explain why certain individuals experienced larger decreases in BP than others (e.g. large standard deviations in Table 4). Nevertheless, when data from all 3 groups were pooled for the first 8 weeks of IHG training, SBP significantly decreased by 9±10 mmHg (p=0.004) and DBP by 5±6 mmHg (p=0.006) highlighting that not only was there a significant change in both SBP and DBP over the first 8 weeks of IHG training, this change represents a clinical decrease in BP defined as of >2 mmHg (Chobanian et al., 2003). As for significant differences between training groups, unfortunately the study was under-powered to detect changes in BP among the smaller sub-groups. However in looking at the data in Table 4, it can be seen that the only group who had additional decreases in BP was the 3 times per week group, while the other groups (0 and 2 times per week) demonstrated increases in BP from mid- to post-testing.

The changes in SBP and DBP in this study are comparable to those of Badrov et al., (2013b) where a medicated hypertensive population performed bilateral IHG training 3 times a week for 10 weeks at 30% MVC. These two studies are comparable in terms of age (65±7 vs. 65±9 years) and baseline SBP (129±16 vs. 133±12 mmHg). However,
these two studies vary in baseline DBP (72±9 vs. 81±9 mmHg), medication and number
of weeks of IHG training. Most of the current study’s participants were taking upwards of
2 BP drugs, (notably 100% of participants were taking β-blockers), whereas Badrov’s
study had a far lower number of individuals medicated (83% medicated) and only one of
which was taking β-blockers. Nevertheless, the results of these two studies align as SBP
was significantly reduced 9 mmHg in this study vs 8 mmHg in the Badrov et al. (2013b),
study. DBP decreased by approximately 5 mmHg in both studies.

As both SBP and DBP were significantly reduced both clinically and statistically,
over 8 weeks of IHG training when participants were pooled, we can conclude that IHG
training is an effective training modality to decrease SBP and DBP among individuals
with medicated HTN.

5.2 Arterial Stiffness

No changes in CCA PP, maximum or minimum diameters or distensibility were
noted. Another IHG study that did not note changes in large artery stiffness (large artery
elasticity index) over a similar training duration and frequency among older hypertensive
individuals was Pagonas et al., in 2017. Other studies however did note changes in
arterial stiffness in response to exercise training. Studies that have found decreases in
stiffness post-training all employed AE as an intervention. A cross-sectional study by
Tanaka et al., (2000) noted that individuals who were more aerobically fit demonstrated
higher arterial elasticity (CCA compliance). Similarly, Monahan et al., (2000) performed
a cross-sectional study comparing both young and older sedentary and endurance-trained
men. It was found that among both sedentary young and older men, their aerobically
trained counterparts displayed both greater CCA arterial compliance and cvBRS.
However, both of these studies employed a measure of habitual exercise over many years, and neither was a shorter controlled exercise trial.

Another study by Monahan et al., (2001) investigated the effects of aerobic exercise on CCA compliance and cvBRS over a 3-month interventional period. Thirteen older men (56±2 years) were prescribed aerobic exercise for 3 months, 40-45 minutes per day at 60-85% maximum HR. Individuals in this study increased their cvBRS by 27% and CCA compliance by 29% with statistically significant increases in measures of cardiovascular fitness (treadmill time to exhaustion, submaximal exercise heart rate). Our population is much older and has higher BP, so they may not adapt in the same manner to IHG training. Furthermore these changes were noted in addition to increased in aerobic fitness, a known confounder of measures of arterial stiffness.

As for PWV measures, among the pooled data for the first 8 weeks of training there were non-significant decreases in upper limb arterial stiffness (crPWV; p=0.095) as well as systemic arterial stiffness (ctPWV; p=0.069). Nevertheless, differences over the 12-week IHG training period were significant for both measures of PWV in all 3 training groups. It should be noted that these changes in PWV occurred in the absence of changes in HR, a known confounder of PWV (Lantelme et al., 2002). As well, changes in ctPWV have been shown to correlate highly with cfPWV the gold standard measure (Philips et al., 2014). Overall, the observed changes in PWV suggest that such training adaptations to IHG may take longer to appear. Since no IHG study has followed participants for a 12-week period, it is possible that these changes require more than the standard 8 weeks of IHG training to become evident. Nevertheless, between group differences were not observed suggesting that the different training frequencies imposed over the last 4 weeks
did not impact the reduction in ctPWV or crPWV measures. Hence, longer follow-up studies need to be conducted to determine the effect of IHG training frequency on PWV.

Decreases in crPWV over time suggest that there may be the potential for a training effect in the trained limb. Schroeder et al., (2017) noted that acute IHG decreased arterial stiffness in the trained limb, however noted that this relationship was only present in older individuals who likely have more collagen and less elastin in their arterial walls and higher BP than their younger counterparts. This study also concluded that changes in arterial stiffness following IHG were likely due to decreases in local sympathetic outflow. No consensus has been reached regarding the mechanism by which IHG reduces arterial stiffness. It should be noted that our study did not measure chronic adaptations of local vasculature SNS outflow nevertheless, the current findings are in agreement with McGowan et al., (2006a, 2006b) and Badrov et al., (2016) in terms of vasculature adaptation in the training limb. However, the current study also found a significant reduction in ctPWV, an indicator of systemic stiffness (Phillips et al., 2014). Without invasively assessing arterial composition and function following IHG training, we cannot comment on alterations in arterial wall composition (i.e., collagen:elastin ratio) or vasodilatory capacity and can only hypothesize the mechanisms underlying the observed changes in stiffness.

5.3 Baroreflex Sensitivity

Contrary to the original hypotheses, there were no changes in measures of HRV or BPV observed in this study. This finding is in agreement with Millar et al., (2013) and Stiller-Moldovan et al., (2012) who both noted no change in measures of cardiac autonomic function (i.e. non-linear HRV and LF-HRV respectively) following IHG
training among individuals with medicated HTN. This finding however is at odds with Taylor et al., (2003) who noted changes in HRV and BPV in individuals with uncontrolled HTN following an IHG protocol. Since our findings agree with other studies on medicated hypertensive populations, it is possible that the pathway in which IHG training has been shown to alter autonomic function may be attenuated by antihypertensive medications, especially since the only study noting changes in ANS function was on a population of both medicated and non-medicated hypertensive populations. As such, individuals with medicated HTN may not have the same capacity to reduce ANS dysfunction as their uncontrolled, unmedicated counterparts.

In addition, no significant change in cvBRS was found in the present study. It should be noted that the study did not reach an adequate sample size to attain power, specifically regarding cvBRS changes. This may have led to increased type II error, which may have contributed to the lack of detection of a significant change. Changes in measures of cvBRS may be particularly hard to detect since they have been shown to display individual day-by-day variability between -50% to +101% and from -58% to +135% in the worst case among clinical populations (Maestri et al., 2009).

6 Strengths and Weaknesses

An overarching strength of the present study is that of the 16 recruited participants, 16 completed the 12-week study. All participants attended the 16 supervised training sessions and performed all 8 at-home training sessions over the initial 8 weeks (100% compliance), all having scored greater than 90% adherence to the training protocol. In the subsequent 4 weeks participants also had 100% compliance to training at
their respective frequencies. Additionally, all participants attended all 3 (pre-, mid- and post-testing) laboratory sessions.

Another strength is that the participants were all taking BP medications (notably 100% of participants were taking β-blockers) and as such were a relatively homogeneous group, despite being at different levels of BP control. All known confounders in the measured demographic data such as BP, age, sex and medication regime were not significantly different between groups at baseline. Additionally, no change in diet, medication regime, or physical activity were noted among any of the participants during the study. While training sessions could not always be conducted at the same time, laboratory sessions were all conducted within 1-2 hours of each other.

One notable weakness of the study design was the lack of a control group. Due to recruitment being difficult in the chosen clinical population, we were unable to recruit enough individuals to form a control group. As such, participants used their baseline values as means for comparison. Also, this study did not employ blinding for either participants or researchers, and as such findings may be affected by expectation bias. Furthermore, sham handgrip training was not performed in the second half of the study to reduce bias. Lastly, as indicated by the power calculation (see Methods section) the current study needed at least 8 participants in each of the 3 groups to adequately detect differences between groups. However, significant reductions were observed for BP and PWV measures over time and thus it is possible that with the addition of more participants, cvBRS changes may become significant.

Due to participant non-compliance (not wearing appropriate attire) and general discomfort with the location of the femoral PP, we were unable to attain cfPWV
measures. While cfPWV is the gold standard measurement of central arterial stiffness, ctPWV has been shown to correlate closely with cfPWV (Phillips et al., 2014). Measurement of PWV itself comes with some limitations including central adiposity increasing the distance component of the PWV calculation. Ultimately, this methodological weakness may have led to erroneously lower PWV values. Furthermore, the CCA PPs were taken on the opposite side of the body from the radial PPs as the finger photoplethysmography cuff was placed on the left side of the body. Nevertheless, the measurement protocol used was consistent across all participants.

7 Future Research

Novel findings from this study suggest several new directions for future research. First, since alterations in BP and PWV were observed in the final 4 weeks of training, these findings indicate that there is merit to investigating the effects of longer IHG training protocols. Additionally in terms of training frequency, this study was underpowered and thus further research into whether 1 training session per week would be sufficient to maintain or produce improvements in the aforementioned variables would be valid. Second, since training effects were seen in only the trained limb in past IHG studies (McGowan et al., 2006a) it would be interesting to see if crPWV were altered in only a trained limb to identify whether IHG has a local, or a more systemic effect on arterial stiffness as both were observed in the present study. Third, since the study did not reach statistical power for cvBRS, a larger cohort should investigate the changes in indices of autonomic function over 8 or more weeks IHG training. Since the literature links changes in local and systemic arterial stiffness, such as those seen in the present study with reductions in SNS activity, it is worth pursuing further to investigate this
relationship in a larger sample. Furthermore, it would be warranted to investigate changes in CCA wall properties over a longer trial to investigate whether IHG can mediate changes.

8 Conclusions

This study aimed to investigate the effect of IHG training frequency among a population of individuals with medicated HTN. Previous literature has demonstrated favourable changes in both BP and trained limb arterial stiffness, but not in systemic arterial stiffness. This study found decreases in SBP following 8 weeks of training 3 times per week and further decreases following a subsequent 4 weeks of training 3 times per week. Notably, BP changes following the initial 8 weeks of IHG training 3 times per week appeared to not be maintained when IHG training was reduced to once per week for a subsequent 4-week period. As well, changes in both regional and systemic arterial stiffness were noted among both the first 8 weeks and continued through the final 4 weeks of training. The changes in BP and arterial stiffness occurred in absence of any changes in CCA distensibility or changes in autonomic function. As such, it may be concluded that the decreases in BP experienced by participants may be driven by more peripheral/systemic vascular changes in response to IHG training. Thus, these results support the prescription of IHG by the ACC/AHA (2017) and CHEP (2017) in the treatment of HTN.
9 References


Appendix A: Information Letter

INFORMATION LETTER

You have been invited to take part in a research study. This letter will outline the purpose of the project, describe the procedures that are required, tell you about potential risks and benefits to yourself, and discuss your rights and confidentiality issues. If you wish to participate, you will be asked to sign a consent form at the end of this letter. Feel free to ask any questions you might have at any time.

Study Title:
Influence of Isometric Handgrip Exercise Training on Cardiovascular and Cognitive Health in Hypertension

Researchers and Contact Information:
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Collaborators
Cheri McGowan, PhD phone: 519-253-3000 ext. 2451 e-mail: mcgowanc@uwindsor.ca

What is the purpose of this study?
In Canada, 1 in 5 people have high blood pressure, or resting blood pressure numbers that are ≥ 140/90 mmHg. Many people taking medicine for high blood pressure do not have their pressures as low as desired (i.e. their blood pressure remains above 140/90 mmHg) and this is a problem. In addition, high blood pressure has been linked to lower cognition and faster rates of cognitive decline as you age.

High blood pressure is commonly associated with greater stiffness of the large arteries and a poorer ability to manage both short and long-term blood pressure. Exposure to high blood pressure over a long period of time (i.e. several years) may lead to worse cardiovascular health and potential impairments in cognitive function.
A new blood pressure management therapy, isometric (constant squeeze) handgrip exercise training lowers resting blood pressure in people with high blood pressure, and even those with well-controlled blood pressure. Squeezing a small handgrip device for 2 minutes, 4 times, 3 days per week for 8 to 10 weeks is now suggested by the American Heart Association as a way to lower blood pressure. This study will look at how this type of exercise affects your blood pressure and the stiffness of your arteries. It also aims to investigate the relationship that blood pressure has with your cognitive health and whether this can be improved as a result of the exercise training.

**Am I eligible?**
This study focuses on men and women diagnosed with high blood pressure who are on a consistent medical regimen.

**Study Inclusion Criteria**
- Resting systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 mmHg
- Currently taking medicine prescribed to lower your blood pressure

**Study Exclusion Criteria**
- Any hospitalization within the past 3 months
- Change in medication within 2 months or over the course of the intervention period
- Physical limitation preventing proper performance of handgrip exercise

**What are the procedures? Will there be any risk involved?**

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

**Visit #1 (approximately 45 minutes):**
You will meet with the study investigators at the Brock-Niagara Centre for Health and Well-Being where you will receive information and consent forms regarding the study. At this time, one of the study investigators will explain all parts of the study, if you are still interested in participating, you will be asked to sign the consent form and fill out a brief medical questionnaire. If you are still eligible, you will then have your blood pressure measured on your upper arm, similar to how it is taken in a doctor's office. Your resting blood pressure and heart rate will be measured after 10 minutes of seated rest and repeated 4 times, with 2-minutes of rest between measures. If your resting systolic blood pressure is ≥140 and/or diastolic blood pressure ≥90 mmHg, your next visit will be scheduled.

**Visit #2 (approximately 45 minutes):**
If you are still interested in participating in the study, and you are initially eligible after Visit #1, you will meet with the investigators again. First, you will have your resting blood pressure measured in the same manner as Visit #1. If your resting systolic blood pressure is ≥140 and/or diastolic blood pressure ≥90 mmHg, you will then practice all parts of the study, including performing the handgrip exercise (four 2 minute squeezes,
separated by 1 minute of rest, and alternating hands after each squeeze). You and the study investigators will then schedule your first laboratory testing day.

**Laboratory Testing Days (approximately 2-3 hours):**

All laboratory testing will take place at the same time of day, in a quiet room located at Brock University in Welch Hall room #22. In total, you will be required to come into the laboratory on 3 occasions throughout the study: Week 0, Week 9, and Week 16. Before each testing session, you will be asked to go to the washroom, as a full bladder can increase your blood pressure. All the procedures involved in the laboratory testing are listed below:

*Body Measurements* which include your height, weight, and waist and hip circumferences will be measured.

*Heart Rate* will be monitored by an electrocardiogram. Two sets of disposable, single-use electrodes will be placed just below each collar bone and on the lower left side near your ribs. There is a very small chance that you might develop a skin rash from the adhesive on the electrodes, but there is no way of knowing if you will be sensitive ahead of time. If a rash develops, the investigators can provide hypoallergenic gel.

*Blood Pressure* will be measured using 2 methods. In addition to the traditional method which involves the arm cuff and stethoscope, a small cuff will be wrapped around the middle finger on your left hand. This cuff will apply a light pressure around the finger, which allows us to measure the blood pressure for each heart beat throughout the study. You should not feel any discomfort. A heating pad might be used to keep your hand warm throughout the test.

*Blood Vessel Imaging* will be performed using ultrasound. The investigator will gently hold the ultrasound tool against the skin at the front of your neck while they take several pictures of 2 of the main blood vessels that lead to the brain (1 on the front region of your neck, and 1 slightly closer to the jaw line). This technique is similar to what is used in hospitals to investigate the heart and blood vessels or to look at a baby during pregnancy. Ultrasound monitoring requires the use of water-soluble, hypoallergenic gel between the probe and the surface of the skin.

*Arterial Stiffness* will be measured using a small pressure pen held against the skin at several locations including the wrist, neck (1 near the middle of the neck and 1 closer towards your jawline), and groin. In addition, a small toe-clip will be placed on your left second toe.

*Cognitive testing* will involve several paper and pencil tasks conducted by the study investigator. For example, you will be asked to remember a list of words, draw objects, trace a trail on paper, and make decisions to solve problems. Some tasks are easy while others are more difficult. It is important to try your best, no matter how easy or challenging you may find them. It is possible that you may feel some anxiety around
completing these tests; however you will have the opportunity to practice before hand and ask any questions you may have.

**24 hour Ambulatory Blood Pressure Monitoring** device will be sent home with you following your laboratory testing sessions. This device will periodically inflate on your arm for a period of 24 hours during which time you are encouraged to go about your normal activities of daily living and avoid strenuous physical activity. The monitor will automatically inflate once every 30 minutes during the day-time and every hour at night-time.

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**Are there any special instructions I should follow when I come in to the lab?**

Yes. On each day of laboratory testing, you are asked to:

- Not perform any **strenuous** physical activity for **24 hours** prior to the laboratory sessions
- Avoid caffeine, alcohol, and nicotine **on the day of** testing
- Eat only a light meal at least **4 hours prior** to the start of testing
- Bring with you a loose-fitting short sleeve shirt and shorts

You will be reminded before each laboratory testing of the requirements listed above.

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**Handgrip Training days (approximately 20 minutes):**

Following the initial Laboratory Testing day, you will be randomly (by chance) allocated to be in 1 of 5 groups. Groups 1 to 4 will be asked to perform 3 handgrip exercise sessions per week, identical to the exercise performed during Visit 2 (four 2 minute squeezes, separated by 1 minute of rest, and alternating hands after each squeeze). Again, these will be performed at 30% of your hardest squeeze on each training day. Two out of 3 weekly training days will be performed at the Brock-Niagara Centre for Health and Well-Being, while the remaining training day may be performed at home. On supervised exercise session days, your blood pressure and heart rate will be monitored before each session, and handgrip exercise will be supervised by an exercise trainer.

If you are in Group 5, you will still visit the centre twice each week to have your blood pressure and heart rate measured. In all groups we will monitor any changes in diet, exercise, and medication on a log sheet which will be provided to each participant and ask that you sign the log at each visit to demonstrate that you still would like to be involved in the study.

Isometric handgrip exercise may result in some tendon soreness of the exercising limb. Measures are in place which minimizes the likelihood of this happening such as alternating hands which perform the contractions. This training protocol has been approved by the American Heart Association and is shown to produce minimal increases in heart rate and blood pressure, even in hypertensive populations. These increases go away quickly and pose no health risk to you. If you experience an adverse reaction,
emergency action plans are set in place and all researchers and assistant will be trained to safely handle the situation.

At the end of the 8 weeks of training (Groups 1 to 4), you will perform handgrip exercise for another 8 weeks. During the second 8 weeks of handgrip training, the number of sessions that you are required to perform each week may be decreased (to 2 or 1 session per week), remain the same (3 sessions per week) or you may stop the exercise altogether. You will be notified how many sessions you will be required to complete. Each week, your resting and ambulatory blood pressure will be monitored. Finally, at the end of the second 8 week period, you will have a final testing day at Brock University (Welch Hall, room #22) followed by 24 hour ambulatory blood pressure measurement.

Will I benefit from this study?
You may or may not experience a lower blood pressure at rest or during your activities of daily living after each part of the study. If handgrip training lowers blood pressure in the people in this study, it may be used by other individuals if their blood pressure is higher than it should be despite taking multiple blood pressure medications.

The handgrip training may result in improved arterial stiffness, short and long-term blood pressure regulation, and cognitive function. While these potential improvements may not be noticeable to you in your daily life, they have a large impact on your cardiovascular health over time.

You will be provided with feedback concerning the average responses of all participants as soon as possible following the completion of the study. A full summary of the study can be made available to all participants within 8 to 10 months following the conclusion of the testing period.

Will I be rewarded for volunteering my time?
You will be provided with free parking on Brock University premises during all laboratory based testing sessions. Secondary monetary compensation will not be provided.

Can I withdraw from the study?
Yes. Your participation in this study is completely voluntary. You may withdraw from the study without penalty or any consequences at any time by making the researchers aware of your decision. Should you choose to withdraw, the confidentiality of your involvement in the study will be maintained and data will be confidentially destroyed. If you do choose to withdraw, in most cases we will ask to use any 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.

Your participation, or lack thereof, in this study will in no way influence your ability to participate in future studies at the Brock-Niagara Centre for Health and Well-Being or Brock University. The investigators may withdraw you from this research if circumstances arise which warrant doing so. Typically, this may occur due to change in medication, nutrition, or physical activity status.
How confidential and secure is my personal information?
Any information that is obtained in connection with this study and that can be identified with you will remain confidential and will not be disclosed at any point in time without your expressed permission. Data will be retained for a period of 5 years following the completion of this study.

To ensure full confidentiality, following your consent, you will be assigned an identification code that can only be linked back to your data by an assigned study investigator. When the data are published in scientific journals or presented at research conferences, they will be expressed as group averages. In the event that individual data will be highlighted, the identification of that person will not be revealed. All paper data will be stored in a locked laboratory cabinet in Welch Hall at Brock University only accessible by study investigators. Digital information will be password protected. All information including medical questionnaires which contain personal identifiers will be destroyed if you choose to withdraw from the study.

Has this study received ethics clearance?
This project has been reviewed and received ethics clearance through the Brock University Bioscience Research Ethics Board (15-065).

We would like to remind you that if you have any questions, you may contact us at any time. Our contact information is on the first and last pages of this letter. Thank you for considering our study.

Sincerely,

Dr. Deborah O'Leary and Liisa Wainman
Department of Health Sciences, Brock University
905-688-5550 ext. 4339
Appendix B: Consent Form

CONSENT FORM

Study Title:
Influence of Isometric Handgrip Exercise Training on Cardiovascular and Cognitive Health in Hypertension

Researchers and Contact Information:
Deborah O’Leary, PhD phone: 905-688-5550 ext 4339 e-mail: doleary@brocku.ca
Liisa Wainman, BSc phone: 905-688-5550 ext 4593 e-mail: lw11au@brocku.ca
Dept of Health Science, Faculty of Applied Health Sciences, Brock University, St Catharines, ON, L2S 3A1. Brock Niagara Centre for Health and Well-Being, 130 Lockhart Drive, St Catharines, ON, L2T 1W5.

Collaborators
Cheri McGowan, PhD phone: 519-253-3000 ext. 2451 e-mail: mcgowanc@uwindsor.ca

Your participation will remain confidential. The personal data collected from this investigation will be kept secured on the premises of Brock University in Dr. O’Leary’s office or laboratory, and will not be accessed by anyone other than the listed investigators.
Investigators will require disclosure of your name and contact information (phone, email), and therefore your participation is not anonymous during the conduct of the research. However, all participants will have their names removed from any data. The master list matching participants to data will be kept by Liisa Wainman (student PI) in a secured room.
I have read the information presented in the information letter about the procedures and risks involved in this study. I have had the opportunity to ask any questions related to the study and have received satisfactory answers. I am aware that I may withdraw from the study without penalty at any time by making the researchers aware of this decision. If I have any further questions about participation in this study I know that I may contact Liisa Wainman, BSc, by phone at 905-688-5550 ext 4593, or by e-mail at lw11au@brocku.ca or Deborah O’Leary, PhD, by phone at 905-688-5550, ext. 4339, or by e-mail at doleary@brocku.ca.
With full knowledge I agree, on my own free will, to be a participant in the research project identified above. I am aware that by signing the consent form, I am not waiving
my legal rights or releasing the investigator(s) or involved institution(s) from their legal and professional responsibilities.

__________________________________________  __________________________________________
Participant (print name)  Participant (signature)

__________________________________________  __________________________________________
Witness (print name)  Witness (signature)

__________________________________________
Date  Location
Appendix C: Medical, Physical Activity, and Educational History Questionnaire

**Personal Information:**
Height: _______ Weight:_______ Date of Birth:______________ Ethnicity:______ Sex: M / F Phone: (___)_________ Postal Code:__________

**Emergency Contact Information:**
Name:________________ Relation:__________
Address:______________________________________________
Phone:(___)______________

**Medical Background:**
Please circle Yes or No for each of the following questions:

Have you ever been hospitalized? Yes No
If yes, please specify.______________________________________________

Have you ever had surgery? Yes No
If yes, please specify.______________________________________________

Are you presently taking any medications or pills (including aspirin, and other over the counter medications)? Yes No
If yes, please specify.______________________________________________

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<tr>
<th>Medication name</th>
<th>Dose</th>
<th>Frequency</th>
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Are you presently taking any vitamins, supplements, and/or herbal supplements? Yes No

Do you have any allergies (medicine, food, bees)? Yes No
If yes, please specify. ______________________________________________________

Have you ever passed out during or after exercise? Yes No
Have you ever been dizzy during or after exercise? Yes No
Have you ever had chest pain during or after exercise? Yes No
Do you have high blood pressure (hypertension) or low blood pressure (hypotension)? Yes No
Have you ever been told that you have a kidney problem? Yes No
Have you ever been told that you have joint instability? Yes No
Have you ever been told that you have a stomach problem? Yes No
Have you ever been told that you have a heart problem? Yes No
Have you ever been told that you have a heart murmur? Yes No
Do you have a machine that regulates your heart rate (pacemaker)? Yes No
Have you ever had racing of your heart or skipped beats? Yes No
Has anyone in your family died of heart disease or sudden death before age 50? Yes No

Do you have Diabetes? Yes No

Do you have asthma or any other breathing related problems? Yes No
If yes, please specify: ______________________________________________________

Do you have any type of cardiovascular disease? Yes No
If yes, please specify: ______________________________________________________

Have you had any other medical problems? Yes No
If yes, please specify: ______________________________________________________

Have you had any other medical problems since your last physical examination? Yes No

Do you currently smoke? Yes No
Have you ever smoked? Yes No
If yes, specify date of smoking cessation: ______________________________________

Do you exercise >30 minutes on ≥2 days per week? Yes No
If yes, please describe your activities _______________________________________

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<th>Exercise</th>
<th>Duration (mins)</th>
<th>Frequency</th>
<th>Intensity</th>
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Are you currently pre-, peri-, or post-menopausal? (Answer post-menopausal if your last menstrual period was over one year ago). Please circle the most appropriate response.
Pre-menopausal  Peri-menopausal  Post-menopausal

If post-menopausal, at what age did you consider yourself menopausal?
________________________________________________________________________

Did you in the past, or do you currently take hormone replacement therapy?
Yes  I am currently on HRT
Yes  I have taken HRT but do not currently
No  I have never taken HRT

**Educational Background:**
Please circle the highest educational ranking achieved:
High School Diploma
College Degree (2 years)
University Degree (4 years)
Graduate Degree (Master's and/or Doctorate)
Appendix D: Isometric Handgrip Training Instructions

HANDGRIP STUDY – AT HOME INSTRUCTIONS

1. Seat yourself in a comfortable position.
2. Using the ZONA handgrip device, press the green power button.
3. Hold the device in your **RIGHT** hand and squeeze as hard as you can. Write this number down on the “*Handgrip Log Sheets*” in your folder.
4. Switch the device to your **LEFT** hand and again, squeeze as hard as you can. Write this number down on the “*Handgrip Log Sheets*” in your folder.
5. Switch the device to your **RIGHT** hand. You will now squeeze at 30% of your earlier maximum squeeze.
   - The device will count down from 120 seconds to zero seconds.
   - You are to hold this contraction for the 120 seconds.
   - This will require you to focus and follow the prompts on the display screen of the ZONA handgrip device.
   - Maintain regular breathing during the handgrip exercise!
6. When the timer reaches zero seconds, you will have 60 seconds to rest and switch the device to your left hand.
7. When the rest period is complete you will follow the same procedure as STEP 5 but now in your left hand.
8. Now, you will perform the same procedures once more in each hand.
9. This should total 2 squeezes in your **RIGHT** hand and 2 squeezes in your **LEFT** hand.
10. When you have completed this, a final number is presented on the ZONA display screen. This is your **COMPLIANCE** score, or the amount of time you spent within 30% of your maximum squeeze for each hand.
11. Write this number down in the “*Handgrip Log Sheets*”
12. At **MINIMUM**, aim to achieve a score of 90.
13. Press and hold the green power button on the ZONA handgrip device for around **5 seconds** to turn the power off.

If you have any questions during your at home exercise sessions, please do not hesitate to contact us.

Liisa Wainman
905-688-5550 x 4593
Lw11au@brocku.ca
Appendix E: Isometric Handgrip Training Log

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<th>Date</th>
<th>What was your maximum contraction value? Right\textsubscript{max}= Left\textsubscript{max}=</th>
<th>What was the final compliance score?</th>
<th>Did you complete 2 sets with each hand?</th>
<th>Have any new medications been prescribed to you? Any new over the counter products?</th>
<th>Have you had any major dietary changes? Physical activity changes?</th>
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