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Getting the Best GRIP on Blood Pressure Control: Are Stress Balls and Computerized Handgrips Equally Effective?

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By

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Declaration of Originality

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Abstract

The World Health Organization (WHO) has identified hypertension (HTN) as a global epidemic, and in accordance, has emphasized the need for cost effective, widely available alternative methods to lower blood pressure (BP) levels in all populations worldwide. Exercise, namely aerobic with dynamic resistance exercise as an adjunct, is a cornerstone method of reducing HTN. Recently, isometric handgrip (IHG) training, has become a formal recommendation of the American College of Cardiology (ACC), and the American Heart Association (AHA) in their recent guidelines. However, traditional IHG requires the use of a computerized dynamometer, which costs upwards of approximately $600 CAD, making the investigation of more cost-effective devices with a high probability for uptake warranted. However, prior to establishing the BP-lowering effectiveness of these devices, the acute stimuli need to be quantified. Therefore, the purpose of this thesis was to compare the heart rate (HR), BP, and rates of perceived exertion (RPE) to a bout of IHG performed using traditional computerized device and a more affordable inflatable stress ball (approximately $4 CAD) among 20 healthy adults with normal BP (average age of 24.70 ± 5.13 years; average resting BP 107.93 ± 16.14/58.68 ± 6.77; average HR 66.01 ± 8.61; 10 women). No statistically significant differences between these two devices were observed with respect to HR, BP, and RPE (all $p > 0.05$). The similar cardiovascular and psychophysical responses between devices provide support for the potential use of the inflatable stress ball as an effective IHG device, and thus, lay the foundation for a future training study.

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Abbreviations

Ach	Acetylcholine
ACSM	American College of Sports Medicine
AHA	American Heart Association
ANP	Atrial Natriuretic Peptide
AOBP	Automated Office Blood Pressure Measurement
ATP	Adenosine Triphosphate
AV	Arginine Vasopressin
Ca^{2+}	Calcium
cAMP	Cyclic Adenosine Monophosphate
CC	Central Command Center
CCC	Cardiovascular Control Center
CVD	Cardiovascular Disease
DASH	Dietary Approach to Stop Hypertension
DBP	Diastolic Blood Pressure
E	Epinephrine
eNOS	Endothelial Nitric Oxide Synthase
EPR	Exercise Pressor Reflex
ET-1	Endothelin-1
IHG	Isometric Handgrip
IL	Isometric Leg
HR	Heart Rate
HTN	Hypertension
K^{+}	Potassium
MAP	Mean Arterial Blood Pressure
mmHg	Millimeters of Mercury
MSNA	Muscle Sympathetic Nerve Activity
NA^{+}/K^{+}	Sodium/Potassium
NE	Norepinephrine
NO	Nitric Oxide
NOS	Nitric Oxide Synthase
nNOS	Neuronal Nitric Oxide Synthase
OBPM	Office Blood Pressure Measurement
PACR	Physical Activity and Cardiovascular Research
PAO2	Partial Pressure of Oxygen
PCAO2	Partial Pressure of Carbon Dioxide
PEH	Post-Exercise Hypotension
PICC	Peripherally Inserted Central Catheter
PKA	Protein Kinase A
PNS	Parasympathetic Nervous System
Q	Cardiac Output
RAAS	Renin Angiotensin Aldosterone System
SA	Sinoatrial
SBP	Systolic Blood Pressure
SNS	Sympathetic Nervous System

SV	Stroke Volume
TPR	Total Peripheral Resistance
WHO	World Health Organization

Chapter 1: Literature Review

1.1 Cardiovascular Disease

Cardiovascular disease (CVD) is the number one cause of death globally (WHO, 2017). CVD is a classification of disorders that affects the heart and blood vessels, and includes coronary heart (artery) disease, cerebrovascular disease, peripheral arterial disease, congenital heart disease, and acute events such as a myocardial infraction (heart attack) or stroke (WHO, 2017). In 2015, over 17 million or 31% of all global deaths were attributed to CVD (WHO, 2017). CVD currently affects approximately 6% of Canadians (7% of men and 5% of women) (Statistics Canada, 2016a). The prevalence of CVD increases with age and affects approximately 18% of Canadians 65 years and older (Statistics Canada, 2016a). In the province of Ontario, CVD was the listed cause for over 136,000 individuals requiring hospitalization in 2012, and contributed to over 24,000 deaths (Public Health Ontario, 2017). At the local level in Windsor-Essex, Ontario, more than 4,000 annual hospital admissions and over 800 deaths per year have been directly attributed to CVD (Public Health Ontario, 2017). These statistics provide evidence of the tremendous impact CVD has in Canada from a national, provincial and local perspective.

The potential for developing CVD can be individually influenced by various modifiable and non-modifiable risk factors. Hypertension (HTN) is one such modifiable risk factor and is the leading cause of CVD, and CVD-related mortality (Ezzati et al., 2002; Daneai et al., 2011; Joffres et al., 2013; Benjamin et al., 2017). HTN accounts for 50% of strokes and 49% of heart attacks globally (Padwal et al., 2016). In Canada, the burden of HTN is high from both a human

and an economic perspective. For example, a population-based study involving 26 million Canadian adults found that all-cause mortality was consistently higher in people of any age who had HTN (Robitaille et al., 2012). Consequently, mortality was 2 to 4 times greater in those aged 20-49 years with HTN, and almost 2-fold greater in those aged 50 years and older with HTN (Robitaille et al., 2012). In 2010, Canada spent approximately 14 billion dollars on HTN-related medical care, equating to over 10% of Canada's overall healthcare costs (Weaver et al., 2015). This expense is projected to increase to over 20 billion dollars by the year 2020 (Weaver et al. 2015). With this projection date only two years in the future, increased understanding of HTN and approaches to reduce the associated prevalence are crucial and timely.

1.2 Hypertension

Blood pressure (BP) is essential to maintain the supply of oxygen-rich blood to working tissues by the arterial system (Tortora, G. J., & Nielsen, M., 2009; McArdle et al., 2010). Arterial BP represents the force exerted by blood on the walls of the arteries during systole (contraction phase of the heart; systolic blood pressure or SBP) and diastole (relaxation phase of the heart; diastolic blood pressure or DBP) after a contraction of the heart muscle (McArdle et al., 2010; Waghmare & Srivastava, 2016). Chronically high BP, or HTN, increases the force exerted on the arterial walls, which strains the cardiovascular system (McArdle et al., 2010), and contributes to neural, hormonal, and vascular dysfunction (Beevers et al., 2001; discussed in Section 1.2.2 on pg. 12). In brief, HTN contributes to over-activity of the sympathetic nervous system (SNS),

increased sodium and water retention, increased vasoconstriction, and increases in blood vessel rigidity (Flammer & Luscher, 2010; El Assar et al., 2013; Thomas & Dasgupta, 2015; see Section 1.2.3 on pg. 25). Over time, HTN can cause damage to arterial vessels, contributing to increased risk for CVD development and a reduced quality of life (McArdle et al., 2010).

Hypertension (HTN) is a global epidemic and in Canada, is the most common chronic condition seen in primary care (WHO, 2013; Finley et al., 2018). In Canada, approximately 7.5 million people are living with HTN, which equates to 1 in 5 adults (Hypertension Canada, 2018). This is a troublesome number as 1 in 5 Canadian adults are also unaware they are living with HTN (Hypertension Canada, 2018). In Ontario during the year 2014, residents with high BP comprised 18.5% of the population, which was higher than the national average of 17.7% (Statistics Canada, 2015a). Similar to CVD, HTN is also more prominent with age, which is concerning as the average age of Ontario's population is 39.8 years, with 14.6% of the population older than the age of 65 years (Statistics Canada, 2015a). By the year 2036, it is projected that older adults (defined as 65 years of age and older) will account for 25% of the population. As HTN occurs at a higher rate in older adults, this may have the potential to result in a higher incidence of people with HTN, impacting Ontarians, and ultimately Canada's, future (Statistics Canada, 2015a). With HTN presently afflicting 1 in 5 people globally, and contributing to 9.4 million deaths related to complications with HTN, prevention and management strategies have come to the forefront in reducing CVD and CVD-related death worldwide (WHO, 2018a).

To understand why an individual may have high BP, HTN can be divided by root cause as either primary (essential) HTN or secondary (non-essential) HTN (Noel & Demper, 1994). Primary HTN accounts for approximately 95% of all cases of HTN and is heterogeneous in nature, with each individual having no definitive cause for high BP (Carretaro & Oparil, 2000). Secondary HTN is associated with specific conditions such as renal, adrenal, or hormonal disorders that cause sustained BP, and in these instances treatment of these conditions usually returns BP to a normal state (Viera & Neutze, 2010).

In both instances, strong relationships exist between high resting BP values and the risk of CVD, renal disease, and mortality (Carretero & Oparil, 2000). Evidence has suggested there is a linear relationship between BP and the incidence of stroke (Lawes et al., 2004; Ishikawa et al., 2007), where a higher level of BP would then increase the risk of incidence. Resting BP values below 120 mmHg SBP and 80 mmHg DBP are considered within a normal range (McArdle et al., 2010; Leung et al., 2017; Nerenberg et al., 2018). Although continually evolving, HTN has traditionally been defined as having a resting BP of ≥140/90 mmHg when using non-automated devices (e.g. sphygmomanometer) (Leung et al., 2017; Nerenberg et al., 2018). Recently, guidelines have included a ≥135/85 mmHg cut-off when using automated office blood pressure (AOBP) devices (Leung et al., 2017; Nerenberg et al., 2018). HTN can be further classified by stages. For years, the stages of HTN have been described as: Stage 1 HTN as 140-159/90-99 mmHg and Stage 2 HTN as ≥160/100 mmHg (Daskalopoulou et al. 2015). However, the American College of

Cardiology/American Heart Association (ACC/AHA) have recently defined more conservative stages of HTN: Elevated (120-129/<80 mmHg), Stage 1 HTN (130-139/80-89 mmHg), and Stage 2 HTN (≥140/≥90 mmHg, Whelton et al., 2018). It is unclear if these newly recommended stages will gain global support.

Although previous guidelines have used the non-automated range for diagnosis, accumulating evidence supports the use of AOBP values ≥135/85 mmHg as a more appropriate diagnostic guideline for HTN (Mancia et al., 2013; James et al., 2014; Leung et al., 2017; Nerenberg et al., 2018; Whelton et al., 2018). Additionally, there is growing evidence to support ambulatory BP as a superior tool for diagnosis, as it measures BP over a 24-hour period (daytime: 6am to 10pm, nighttime: 10pm to 6am, mean 24-hour) (Pickering et al., 2005; Leung et al., 2017; Nerenberg et al., 2018). Using ambulatory measures, HTN is defined as mean awake BP of ≥135/85 mmHg or mean 24-hour BP of ≥130/80 mmHg (Leung et al., 2017; Nerenberg et al., 2018). Most individuals will have their highest pressures in the morning and lowest pressures at night, with the onset of sleep, decreasing BP by decreasing metabolic activity (Pickering, 1990). These BP measures taken at night can be used to examine “dipping status” (explained further in Section 1.2.1 on pg.7), or the gradual decrease in BP seen at the onset of sleep, where dipping <10% of their awake BP average would be classified as non-dipping (Pickering, 1990; Mancia & Verdecchia, 2015). This phenomenon of non-dipping has been shown to be present in hypertensive individuals and is associated with sleep apnea, diabetes, congestive heart failure, orthostatic hypotension, and Cushing’s syndrome (Pickering, 1990). While there

are many advantages to ambulatory measurement, non-automated and automated measures are common for clinical use as they are time and cost efficient (Pickering et al., 2005).

1.2.1 Blood Pressure Measurement

As briefly mentioned in Section 1.2 above, BP measurement is integral to the effective diagnosis and treatment of HTN. The most accurate measure is completed via insertion of a catheter equipped with a transducer into the radial artery measuring beat-to-beat systolic, diastolic, and mean arterial BP (Parati et al., 1989). Although this procedure remains the most accurate method, it is both costly and higher risk, requiring specialized training and personnel to perform correctly (Parati et al., 1989). Alternatively, there are other methods of measuring BP including: the non-automated method of auscultatory sphygmomanometry, and automated oscillometric methods (Pickering et al., 2005). Each of these methods involve occlusion of the brachial artery and are recommended in recent guidelines for BP measurement (Dasgupta et al., 2014; Leung et al., 2017; Nerenberg et al., 2018).

Auscultatory Sphygmomanometry

Auscultatory sphygmomanometry is used in office BP (OBP) measurement and performed by placing a cuff around the arm and inflating the cuff to a supra-SBP to collapse the brachial artery (Perloff et al., 1993). As the cuff gradually deflates, the appearance and disappearance of sound generated by arterial pulse waves, or Korotkoff sounds, determine the SBP and DBP, respectively (Perloff et al., 1993; Pickering et al., 2005).

There are several important limitations associated with this method that may influence its accuracy. For example, the level of skill of the practitioner identifying the Korotkoff sounds (Pickering et al., 2005), age-related hearing loss, decreased focus over long shift periods, parallax error (where BP could be over or underestimated based on the angle the practitioner is viewing the sphygmomanometer (Williams et al., 2009), and observer biases (practitioner altering results based on existing relationships) (Pickering et al., 2005; Sechrest et al., 2005) all play a role in obtaining accurate measurements. The device itself also has limitations, as cuffs that are larger in comparison to an individual's arm may need more pressure to cause occlusion, which can also impact results (Sechrest et al., 2005). Although this method is convenient and time efficient, the collective limitations can lead to a misdiagnosis or an undiagnosed case of HTN (Pickering et al., 2005). Evidence has also shown that measurements taken via auscultatory sphygmomanometry are typically higher on average compared to automated methods (Myers et al., 2010). This may be due to white coat HTN, in which the presence of a clinician will increase the patient's BP unintentionally, producing inaccurate readings of his or her true BP (Myers et al., 2010). This phenomenon is mitigated by using both oscillometry and ambulatory BP methods (Myers et al., 2010).

Oscillometry

Recently, oscillometric methods have become the preferred method for measuring and assessing resting BP, contributing to the popularization of AOBP measurement (Mancia et al., 2013). Similar to auscultatory sphygmomanometry,

oscillometry also uses occlusion of the brachial artery by an inflatable cuff (Alpert et al., 2014). However, a microprocessor within the device is used to detect the SBP and DBP via oscillatory signals (Alpert et al., 2014). Oscillometry does not involve the use of Korokoff sounds, but rather measures the amplitude of oscillometric pulses from the brachial artery (Alpert et al., 2014). The cuff inflates from 160 to 180 mmHg (for normotensive, inflation adjusts to be greater than SBP) for an adult individual and will be deflated in a controlled release via a small valve (Alpert et al., 2014). This controlled automated release then produces the oscillatory signals, which the microprocessor uses to create an estimate for mean arterial pressure (MAP) (Shahriari et al., 2003). Using the MAP in conjunction with the built-in algorithms, SBP and DBP are determined (Shahriari et al., 2003). HTN is determined at a lower range of ≥ 135/85 mmHg with this device due to the accuracy when compared to auscultatory sphygmomanometry, and recently this range has become a new diagnostic standard (Leung et al., 2017; Nerenberg et al., 2018; Whelton et al., 2018). This method can also be used to reduce the effects of white coat HTN (Myers et al., 2010; Myers et al., 2014). Home BP measurement is now a unique testing method, whereby AOBP is determined using a device in the patient's own home by the patient themselves (Myers et al., 2010; Myers et al., 2014). Research has shown that in both instances BP values are commonly seen to be lower than when acquired in clinical settings (Myers et al., 2010; Myers et al., 2014).

Although this method requires less training time and has fewer interpersonal variations, a prominent concern is the variability between

oscillometric devices as different manufacturers use differing algorithms (Pickering et al., 2005; Alpert et al., 2014). As these specific algorithms are undisclosed between companies, results may differ between one individual and multiple AOBP models (Pickering et al., 2005; Alpert et al., 2014). Oscillometric methods may also be impacted by different factors that may influence detection of oscillometric signals within the cuff, one factor being arterial stiffness prominent in older individuals and may underestimate MAP, ultimately impacting SBP and DBP values (Pickering et al., 2005; Harvey et al., 2015). Another factor that may impact potential diagnosis is incorporation of home BP monitoring. This may also provide an accurate BP reading by reducing white coat HTN, as noted above, but automated home models introduce reporting bias into the diagnosis process (Myers et al., 2014). Reporting bias is when the patient responsible for reporting their BP results does so incorrectly based on his or her intentions (e.g. a patient who does not want to take HTN medication may report lower readings vs. a patient who has concerns about HTN risks may embellish their readings) (Myers et al., 2014). Reporting bias can be reduced via a machine that transmits results directly to the office (Myers et al., 2014). However, this added feature increases the cost effectiveness of home BP, which reduces the accessibility of this method (Myers et al., 2014). Despite the limitations AOBP, when it is compared to intra-arterial and auscultatory methods, in accordance with updated guidelines, it is regarded as an accurate method of measuring BP (Pickering et al., 2005; Alpert et al., 2014; Mancia et al., 2013; Leung et al., 2017; Nerenberg et al., 2018).

Ambulatory Blood Pressure

Unlike sphygmomanometry or oscillometry that are typically constrained to a small number of readings in a clinical setting, ambulatory BP monitoring is used to collect BP readings several times over a 24-hour period (Turner et al., 2015). The measurement process is similar to the preceding methods as it involves a cuff being placed around the upper arm to measure BP at the brachial artery using oscillometric methods of BP calculation (O'Brien et al., 2001). The cuff is then connected to a monitor by an inflationary hose, which is programmed to measure BP (O'Brien et al., 2001). In this 24-hour period, BP is normally assessed every 30 minutes during the day (6am to 10pm), and every hour during night (10pm to 6am), which establishes BP means for different time periods (i.e. full 24-hours, daytime BP, nighttime BP) (Pickering et al., 2005; Turner et al., 2015). This continuous measure of BP provides a superior prediction of cardiovascular risk when compared to the brief time periods measured from other methods (Turner et al., 2015). This advantage can also be attributed to the BP measurements being acquired during an individual's daily activities, showing a broader range of BP changes, and providing a truer representation of BP (Turner et al., 2015). Nighttime measurements are of particular importance as, normally (excluding those who work midnights, where these same hours are spent awake), individuals will have a dip in BP from 10% to 20% of their average daytime BP (Su et al., 2008; Turner et al., 2015). Those who dip less than 10% are deemed "non-dippers" and are at a greater risk of developing HTN, sleep apnea, diabetes, congestive heart failure, orthostatic hypotension, and Cushing's

syndrome (Pickering, 1990; Turner et al., 2015). This dip in BP is due to a reduction in SNS activity and an increase in PNS function, which reduces plasma epinephrine (E) and norepinephrine (NE) (Turner et al., 2015). However, conditions like sleep apnea can stimulate greater sympathetic outflow due to a lack of blood oxygen, which in turn increases BP by increasing SNS activity (Fletcher, 2001). Ambulatory measurement can detect this increased diurnal BP, providing evidence that BP measurement for 24-hour time periods provides a greater understanding of an individual's BP profile.

Ambulatory BP measurement has the benefit of portability allowing for the collection of data outside of the clinical setting (Pickering et al., 2005). However, this method does have its limitations. As ambulatory monitoring employs oscillometry, as noted above, the algorithms for determining BP differ from manufacturers (Pickering et al., 2005). Moreover, if an individual does not remain still during each BP measurement completed, or if the individual removes the cuff for bathing and reequips it incorrectly, insufficient results may be produced and ultimately lead to an improper assessment (Pickering et al., 2015). Despite these disadvantages, ambulatory BP measurement is superior in accuracy when compared to traditional methods (Myers et al., 2010; Myers et al., 2014).

1.2.2 Blood Pressure Regulation

Before understanding elevated BP levels and HTN pathophysiology, it is important to understand the mechanisms of BP control under normal conditions. Cardiovascular homeostasis is maintained by the regulation of several key physiological mechanisms including BP, amount of oxygen content within the

blood, and blood volume (Dampney, 2016). Cardiovascular homeostasis is important as it must be maintained to deliver oxygen to the working tissues (Dampney, 2016).

To fully comprehend BP, the influencing components must be understood. BP is the sum of cardiac output (Q) and total peripheral resistance (TPR; see Equation 1), where, Q is the amount of blood pumped per contraction of the heart and TPR is the resistance of the vessels to the flow of blood (Waghmare & Srivastava, 2016). Cardiac output (Q) can be broken down further into stroke volume (SV) and heart rate (HR), where SV is the amount of blood ejected by each ventricle per contraction of the heart and HR is the number of heart beats per minute (see Equation 2) (McArdle et al., 2010).

Equation 1: BP = Q x TPR

Equation 2: Q = SV x HR

Although BP may be broken down into the variables of Q and TPR, numerous interrelated neural, hormonal and local pathways govern Q, TPR, HR, and SV in an effort to maintain BP, and thus equilibrium (McArdle et al., 2010).

Neural Blood Pressure Regulation

BP is controlled neurologically by the autonomic nervous system (ANS), which is comprised of the SNS and the parasympathetic nervous system (PNS) (McArdle et al., 2010). Sympathetic nerves innervate the heart and blood vessels, both of which are predominately regulated by sympathetic premotor neurons located in the lower brain stem, while the hypothalamus and vagal parasympathetic nerves innervate the heart and originate from the nucleus

ambiguous in the medulla oblongata (Dampney, 2016). The purpose of the SNS is to increase HR and myocardial contractility to facilitate an increase in SV, increasing vasoconstriction to improve venous return, and increasing blood flow to working tissues via vasoconstriction of the vascular beds of organs and uninvolved tissue (Nobrega et al., 2014). The opposite is true of the PNS, as activation causes a withdrawal of sympathetic activity, decreasing HR, decreasing TPR, and vasodilation of vascular beds where BP was previously reduced by vasoconstriction and SNS activity (Nobrega et al., 2014). For example, during exercise, PNS activity is reduced to then increase SNS activity to deliver oxygen-rich blood to working tissues by increases in HR, SV and TPR (Nobrega et al., 2014).

Two key areas of the brain that co-ordinate ANS action are the central command (CC) centre and the cardiovascular control centre (CCC) (Victor et al., 1995). The CC will respond to cardiovascular stress via transmission of efferent signals to the CCC (Michelini et al., 2015). Circulatory control is governed by two principles: i) the CC sets the basic pattern of motor activity to skeletal muscles and drives cardiorespiratory stimulation, and, ii) the feedback control mechanisms are driven by intrinsic/extrinsic receptors from cardiovascular areas and receptors within the active muscles and surrounding vasculature (Michelini et al., 2015). At the onset of physical activity (e.g., limb movement related to shifting from a seated position to standing), afferent signals from the body relay information to the CC via a multitude of negative feedback loops (e.g. increases in Q, changes in TPR, muscle contraction) (Michelini et al., 2015). The CC then

activates the CCC, which alters activity to the nerves that innervate the heart and blood vessels through sympathetic and parasympathetic mechanisms, ultimately influencing BP (Michelini et al., 2015). To achieve this feedforward response, the CC and CCC work in concert with feedback neural controllers located in the periphery, which consist of baroreceptors, chemoreceptors, and skeletal muscle receptors, to regulate BP (Michelini et al., 2015).

The baroreceptors are stretch receptors located in the walls of the carotid sinus and aortic arch, which provide information regarding the BP in the vessels entering the brain and leaving the heart (Wehrwein & Joyner, 2013; Dampney, 2016). Baroreceptors operate around a central point of BP (Osborn et al., 2005). When the artery is distended beyond a set point, there is an increase in afferent firing of signals to the CC (Wehrwein & Joyner, 2013). This signal is then relayed by both the SNS (innervation of the blood vessels and heart), and the PNS (innervation of the pacemaker cells of the sinoatrial node) (Wehrwein & Joyner, 2013). The response is made by the CCC to inhibit SNS activation, reducing TPR, HR, and thus Q, and acting to ameliorate deviations from the central point of BP (Taylor et al., 2014). This return of BP to the set-point range by SNS suppression and PNS activation, slowing the heart and increasing vasodilation of peripheral tissue is known as the arterial baroreflex (McArdle et al., 2010; Dampney, 2016). Inversely, the opposite stimulus would elicit a similar response by the arterial baroreflex. With a drop in BP, afferent signaling would cause the CCC to increase SNS activation and PNS inhibition, increasing TPR, HR, and Q,

thus increasing BP to the central point (Michelini et al., 2015; Dampney et al., 2016).

Chemoreceptors are located in the carotid and aortic arteries and become activated by a change in partial pressure of oxygen in the arterial blood (PaO_2), partial pressure of carbon dioxide in the blood ($PaCO_2$), and pH content in the blood (H+ ions) (Gordan et al., 2015; Dampney, 2016). For example, if there is a drop in PaO_2 and a rise in $PaCO_2$ and H+ ions, the physiological response through activation of this reflex is to increase respiratory rate and depth (to increase alveolar ventilation) and increase BP to peripheral tissues that also increase HR and Q to meet the demand of oxygen needed by those tissues (Gordan et al., 2015; Dampney, 2016). An example of how chemoreceptor activity occurs can be seen in sleep apnea (Fletcher, 2001). Sleep apnea is a condition that reduces oxygen in the body during sleep caused by pauses in breathing (Fletcher, 2001). As a result, chemoreceptors sense this decrease in oxygen, which causes an increase of afferent signal firing to CC, and subsequent CCC-generated increases in SNS activity (Fletcher et al., 2001; Gordan et al., 2015). This enhanced SNS activity increases vasoconstriction of vascular beds and ventilation to upregulate oxygen, thus increasing BP (Fletcher, 2001; Gordan et al., 2015; Michelini et al., 2015).

There are also receptors located within skeletal muscle that help to control BP. The two main afferent receptors in this location that have an influence on BP are the type III mechanoreceptors and the type IV metaboreceptors (Leshnower et al., 2001). Mechanoreceptors sense stretch and conformational changes in the

arterial walls as a by-product of movement (similar to the baroreceptor) (Leshnower et al., 2001). Metaboreceptors respond to the accumulation of metabolic by-products of the working muscle such as lactic acid, potassium (K+), bradykinin, serotonin, and adenosine (Leshnower et al., 2001). During movement, muscle contractions cause stimulation of the mechanoreceptors, and when the oxygen demands of the muscle are not met along with by-product accumulation, metaboreceptors are activated (Belli et al., 2011). BP is controlled by afferent impulses from these receptors being transmitted to the CC, which then drives SNS to cause increases in ventilation and vasoconstriction of less involved vascular beds (Leshnower et al., 2001; Belli et al., 2011). This in turn will then cause a rise in BP through an increase in TPR, HR, and Q to meet demands of working tissue (Belli et al., 2011).

Hormonal Control of Blood Pressure

Both the SNS and the PNS are involved with the release of hormones in response to changes in BP homeostasis via parallel pathways. These hormones include epinephrine (E), norepinephrine (NE), acetylcholine (ACh), vasopressin, renin-angiotensin-aldosterone system (RAAS), and atrial natriuretic peptide (ANP) (Gordan et al., 2015).

The main catecholamines that activate or deactivate sympathetic receptors in the cardiovascular system are E and NE (Gordan et al., 2015). These neurohormones accelerate sinoatrial node depolarization, causing the heart to beat faster (tachycardia), along with increasing myocardial contractility (McArdle et al., 2010). The force and rate of ventricular contraction will nearly

double under maximum sympathetic stimulation (McArdle et al., 2010), efficiently delivering oxygenated blood to working tissue. Postganglionic sympathetic nerve fibres extend to the smooth muscle layers of small arteries, arterioles, and precapillary sphincters located in target organs to regulate BP (McArdle et al., 2010). These sympathetic nerve fibres contain E and NE receptors, that when stimulated through binding of catecholamines, alter BP effectively (McArdle et al., 2010). There are two types of E and NE receptors located in these areas to induce changes, which are α-adrenergic and β-adrenergic receptors (Gordan et al., 2015). The α-adrenergic receptor group are separated into α_1-adrenergic receptors located in most sympathetic target organs (excluding the heart), and α_2-adrenergic receptors found in synaptic junctions of SNS nerve endings of vascular beds (Gordan et al., 2015). The β-adrenergic receptors are also separated into two main types. β_1-adrenergic receptors are located in the heart, lungs, kidneys, and adipose tissue, while β_2-adrenergic receptors are found in most sympathetic organ targets (Gordan et al., 2015). Sympathetic stimulation of α-1 and α2-adrenergic receptors induces vasoconstriction and stimulation of β2-adrenergic receptors causes vasodilation (McArdle et al., 2010; Gordan et al., 2015). Vasoconstriction and vasodilation manipulate the diameter of the blood vessel to adjust TPR (McArdle et al., 2010; Gordan et al., 2015). Vasoconstriction reduces the diameter of the blood vessel, increasing TPR and BP, while vasodilation will increase the diameter of the blood vessel, facilitating decreases in TPR and BP (McArdle et al., 2010).

Unlike the SNS, the PNS promotes relaxation and vasodilation, accomplished by release of the hormone ACh (McArdle et al., 2010). There are 5 different muscarinic receptor subtypes in the body, of these receptors, the M2 receptor is located in the heart and is the main binding site for ACh (Brodde et al., 2001). Stimulation of the M2 receptor has both chronotropic (effects that change HR) and inotropic effects (activation or deactivation of ion channels) in the atria, but only inotropic effects in the ventricle (Brodde et al., 2001). A decrease in HR occurs when ACh binds to the receptors on the sinoatrial node (chronotropic) and the atrioventricular node (inotropic), causing an inhibitory effect on adenyl cyclase, which then reduces intracellular cyclic AMP (cAMP) (Brodde et al., 2001; McArdle et al., 2010). This interaction causes a reduction of L-type calcium (Ca_2+) current, which a constant influx of Ca_2+ is needed for contractions of the heart (Brodde et al., 2001). This reduction of cAMP by binding of ACh is a regulatory mechanism of the PNS to reduce the force of contractions in the heart, resulting in a decrease in HR, thereby lowering Q and BP (Brodde et al., 2001). In this case, the purpose of the PNS is to reduce the sympathetic effects of the catecholamines, bringing the body back to homeostasis, or normal resting BP. This action is parallel to the baroreflex activity that occurs when there is an increase in BP, as sensory information relayed to the CC then is transmitted and acted upon by reducing SNS activity and increasing PNS activity.

Similar to the BP effects of E and NE, vasopressin will act to increase BP, but through fluid retention. Vasopressin release is triggered by the baroreceptor reflex (decrease in BP), chemoreceptors (decrease in blood oxygen), as well as

decreases in blood volume (Japundzic-Zigon, 2013). Vasopressin affects the kidney's filtration system by increasing reabsorption of water in the collecting tubules of the kidneys, effectively increasing blood volume, and thus, BP (Gordan et al., 2015). Vasopressin's action can be examined during exercise, as at higher exercise intensities the body will sweat to reduce surface temperature, thus, cooling the body (McArdle et al., 2010). In this instance, there may be significant fluid volume loss, which increases blood viscosity and the potential for dehydration (McArdle et al., 2010). Vasopressin is released to maintain adequate fluid balance in blood and reduce the decreases in BP, blood volume, and increases in plasma osmolality seen with sweating. BP to working tissues is thus maintained by adequate fluid balance in combination with an increase in TPR by vasoconstriction of major blood vessels (McArdle et al., 2010).

Parallel to vasopressin, the RAAS becomes active when the body is in a state of hypovolemia and is triggered by a series of actions as followed: when baroreceptors detect a decrease in BP (in this case from reduced blood volume), when there is a decrease in blood concentrations of sodium chloride (i.e., salt), and, when there is a lowered rate of blood flow through the macula densa (located in the ascending loop of Henle just before the transition to the distal convoluted tubule in the kidney) (Gordan et al., 2015). The onset of decreased blood volume triggers the release of renin by the kidneys to transform angiotensinogen into angiotensin I, which is then converted into angiotensin II via angiotensin converting enzyme (Gordan et al., 2015). The product of angiotensin II is important as it has a direct effect on the cardiovascular system (Fyhrquist &

Saijonmaa, 2008). Angiotensin II stimulates angiotensin type 1 (AT1) and type 2 (AT2) receptors to alter BP (Mehta & Griendling, 2007; Fyhrquist & Saijonmaa, 2008). Activation of AT1 receptors is associated with sympathetic activation and release of E and NE, as it causes a generalized vasoconstriction, increasing TPR in the renal arteries and the afferent/efferent arterioles (Gordan et al., 2015). Angiotensin 1 (AT1) vasoconstriction is most dominant in arteries to the internal organs, diverting blood to skeletal muscle for increased oxygen delivery (Gordan et al., 2015). Angiotensin 1 (AT1) stimulation also increases sodium (Na+) reabsorption (which passively acts on water reabsorption) and is the precursor to aldosterone release from the adrenal cortex, which also increases Na+ intake (Mehta & Griendling, 2007). This increase in TPR via vasoconstriction combined with an increase in blood volume by sodium and fluid retention will cause a rise in BP. However, in contrast, when angiotensin II is bound to AT2 it counterbalances the effects of AT1, as AT1 is excitatory and AT2 is inhibitory. Angiotensin II is more likely to bind to AT2 receptors at higher blood concentrations, which stimulation will cause vasodilation, thought to be predominantly caused by nitric oxide (NO) release (a potent vasodilator discussed in further detail below) (Mehta & Griendling, 2007; Fyhrquist & Saijonmaa, 2008; Carey & Padia, 2013). Research regarding AT2 is relatively new when compared with that of AT1. However, it is hypothesized that AT2 receptors play a large role in natriuresis and diuresis, or secretion of sodium and water, respectively, via the kidneys (Carey & Padia, 2013). Equilibrium is maintained once angiotensin II has saturated AT1 receptors (Carey & Padia, 2013). It has also been theorized that angiotensin II

could be converted to angiotensin III, which then binds to the AT2 receptor to balance the effects of AT1 (Carey & Padia, 2013). Although research is growing with regards to this topic, AT2 receptors need to be examined further to uncover the true physiological effects.

Atrial natriuretic peptide (ANP) is secreted primarily from the atrial myocytes in response to increased angiotensin II, β-adrenergic receptor stimulation, and intravascular volume changes, which causes a localized stretch on the walls of the atria sensed by mechanoreceptors (Brenner et al., 1990). ANP secretion is also influenced by ACh, E and vasopressin (Brenner et al., 1990). The central functions of ANP are to promote natriuresis and diuresis (excretion of Na+ and water) in the kidneys, in combination with vasodilation to reduce BP (Song et al., 2015). Vasodilatory properties of ANP can be observed during hypoxia, as ANP will be secreted to increase oxygen delivery back to the heart and to cause vasodilation in peripheral arteries to reduce BP (Dietz, 2005). Natriuresis and diuresis is accomplished by ANP through increases of cyclic guanosine monophosphate-dependent protein kinases (PKGs), which increases glomerular filtration, inhibits sodium and water reabsorption, and suppresses secretion of renin, which is the hormonal precursor for RAAS activation (Zeidel, 1990; Theilig & Wu, 2015). Decreases in Q are also related to ANP mediated sympathetic and parasympathetic activity. ANP causes hypotension and suppresses the stimulatory effects of baroreceptor activation, which then reduces sympathetic activity and drives parasympathetic activity (Brenner et al., 1990). Relaxation of vascular smooth muscle cells then occurs by lowering intracellular

levels of Ca^{2+} and decreasing the vessel sensitivity to Ca^{2+}, thus causing vasodilation (Carvajal et al., 2000). In summary, ANP lowers BP by reducing TPR through vasodilation of the peripheries and heart, excretion of sodium and fluid (reducing the total blood volume), and via reductions in HR (Song et al., 2015).

Local Control of Blood Pressure

Working tissues release substances that are produced via increased metabolic demands, and these locally produced components help to regulate BP. During neural and hormonal regulation mechanisms, metabolic by-products are released from each pathway that may also aid in BP regulation locally (Beevers et al., 2001). Endothelial cells release local agents in response to increases in blood flow and shear stress caused by blood on vascular endothelium (McArdle et al., 2010). These regulators function to alter smooth muscle diameter through vasoconstriction and vasodilation and include: K+, NO, and endothelin-1 (ET-1), which may all work simultaneously to maintain homeostasis (McArdle et al., 2010).

Potassium (K+) is an abundant intracellular ion, which is used to create action potentials in a neuron (Haddy et al., 2006). The Na+-K+-ATPase pump helps to create action potentials by pumping K+ out of the plasma membrane and Na+ into the membrane (Haddy et al., 2006). When a muscle tissue becomes active, action potentials are created to meet the demands of the exercising tissues (Haddy et al., 2006). Due to the unequal nature of the pump an accumulation of K+ occurs resulting in hyperpolarization of the membrane

(Haddy et al., 2006). In this instance, this hyperpolarization causes a reduced Ca_2+ influx into the cell, which then causes a dilation of the arteriole (Haddy et al., 2006). When there is a reduction of Ca_2+, the blood vessels in the surrounding area have difficulties maintaining an increased TPR, as Ca_2+ is needed for the contraction of the endothelium (Haddy et al., 2006). TPR is then reduced as vasodilation occurs in the area of increase K+ concentrations, which reduces BP locally.

Nitric oxide (NO) is involved in various physiological processes and is continually synthesized by two different NO synthases (NOS), which are neuronal NOS (nNOS) and endothelial NOS (eNOS) (Lundberg et al., 2008; Lundberg et al., 2015). L-Citruline and NO are formed by eNOS and specific physiological cofactors (for example, reduced tetrahydrobiopterin or BH4) in the endothelium as a response to mechanical stimuli (Lundberg et al., 2008; Lundberg et al., 2015). NO diffuses into the underlying smooth muscle cells, which then will generate cyclic guanosine monophosphate (cGMP) (Lundberg et al., 2015). This process has a vital role in regulation of vascular tone and endothelial integrity as it causes vasodilation (Lundberg et al., 2015). NO will potentially pass through underlying cell membranes to neighbouring arterial walls to expand the vasodilatory effects (McArdle et al., 2010). TPR is then modified by increasing blood flow to tissues by gradually altering the arteriole size of surrounding tissues, effectively reducing BP.

Endothelial cells release ET-1, a vasoconstrictor, which counterintuitively is not stored in these cells (Chester & Yacoub, 2014). Release of ET-1 is

dependent on mechanical stimulation (shear stress), hypoxia (reduced environmental oxygen), reduced levels of estrogens, glucose, thrombin, and competing vasoconstrictors (Chester & Yacoub, 2014). Factors that reduce the synthesis of ET-1 include increases in NO, ANP, and estrogen (Chester & Yacoub, 2014). Once synthesis of ET-1 occurs, ET-1 will bind to designated receptors located on vascular smooth muscle cells (Chester & Yacoub, 2014). ET-1 has three main binding sites in relation to BP regulation. When ET-1 binds to ET_A or ET_{B2} it causes vasoconstriction of the smooth muscle, increasing TPR and BP (Gordan et al., 2015). When ET-1 is bound to ET_B NO is released to facilitate vasodilation and decrease TPR and BP (Gordan et al., 2015). Vasoconstriction is also modulated through the stimulation of protein kinase C (PKC), and through an influx of calcium into the cell to facilitate contraction of the muscle (Chester & Yacoub, 2014).

1.2.3 Pathophysiology of Hypertension

Adequate BP control is reliant on the balance of Q and TPR with increases in one or both factors leading to the development and maintenance of HTN (Beevers et al., 2001). The specific mechanisms for these increases remain unclear, and are likely multifaceted and complex. HTN development is purportedly linked to dysfunction in one or more of the neural, hormonal, and local mechanism(s) that regulate systemic BP, and enhanced via a plethora of risk factors (Beevers et al., 2001).

From a neural perspective, SNS over activity has been implicated in the development of primary HTN (Mancia et al., 1999; Beevers et al., 2001; Manolis

& Poulimenos, 2014). Elevated SNS activity increases the likelihood of HTN development through stimulatory effects on the cardiovascular system and kidneys to create increases in Q and TPR (Parati & Esler, 2012). In persons with established HTN, NE (see Section 1.2.2 for details, pg.12) is released in larger amounts, binding to adrenergic receptors and maintaining HR in an elevated state (Mancia et al., 1999), increasing Q and BP. Individuals with primary HTN have a higher SNS activity level than their normotensive counterparts (Thomas & Dasgupta, 2015). Grassi et al., (1998) demonstrated that with increasing stages of HTN, there was a markedly increased level of SNS activity. Researchers suggested that increased levels of plasma NE causes increased sympathetic outflow to the heart and kidneys (Fischer & Paton, 2012; Parati & Elser, 2012; Manolis & Poulimenos, 2014; Thomas & Dasgupta, 2015; Grassi & Ram, 2016). This increased sympathetic outflow increases HR, Na+ retention, and water retention via sympathetic denervation of the heart and renal tubules (Thomas & Dasgupta, 2015).

Hypertension (HTN) is also a product of augmented sympathetic outflow to the kidneys, which affects the RAAS system (Grassi & Ram, 2016). Increased sympathetic activity to the juxtaglomerular cells cause an increase in renin release, which increases angiotensin II and impairs renal vasodilation (Thomas & Dasgupta, 2015; Grassi & Ram, 2016). This then upregulates aldosterone release, altering BP by augmenting retention of Na+ and fluids (passively), which together cause an increase in BP via vasoconstriction and elevated blood volume (Beevers et al., 2001; Singh et al., 2010; Thomas & Dasgupta, 2015).

At the local level, the endothelium can be examined as a contributor to HTN. Endothelium is the inner most layer of the vascular wall, which healthy endothelium is characterized by vasodilatory, anti-inflammatory, and anti-thrombotic responses as described previously (see Section 1.2.2 pg.12). However, dysfunctional endothelium has a decreased response to local regulators of BP, in particular, the prominent vasodilator NO (Flammer & Luscher, 2010). This reduced efficacy affects vascular function by reducing vasodilatory response, and this has been observed in hypertensives and those with a family history of HTN (Panza et al., 1990; Taddei et al., 1992; Flammer & Luscher, 2010).

A decreased bioavailability of NO, due to interaction with reactive oxygen species (ROS), may also facilitate HTN development and maintenance (Flammer & Luscher, 2010). Superoxide anion (O_2^-), which is a common form of ROS, can then transform NO to peroxynitrite ($ONOO^-$) to reduce the bioavailability of NO (Spieker et al., 2000; Sindler et al, 2009; Harvey et al., 2015). Peroxynitrite ($ONOO^-$) oxidizes tetrahydrobiopterin (BH4), an essential cofactor (a substance that is essential for an enzyme's activity) for NO synthesis by eNOS, to an inactive form effectively reducing NO production (Sindler et al., 2009; Harvey et al., 2015). NO, as noted above, is a key factor for vasodilation as it modifies TPR passively by interacting with arterial walls, and without this effect of NO, BP will steadily increase as its availability is reduced (Sindler et al., 2009). However, this is not the only culprit hypothesized to increase BP at the local level.

Endothelin 1 (ET-1), a local vasoconstrictor to the endothelium (described in Section 1.2.2 pg.12), may be increased in the plasma and is proposed to be from increases in dietary salt, which increases the sensitivity of the renal tubules to other stimuli that facilitate ET-1, like hypoxia (Heimlich et al., 2015). The connection between a high dietary salt intake and the role of ET-1 increasing BP has also been linked to the reduction of NO bioavailability through activation of NADPH oxidase (NADPH oxidase is a membrane bound enzyme that transfers electrons from the NADPH molecule that is a byproduct in energy production), which also increases the production of ROS (Heimlich et al., 2015). Loomis et al., (2005) observed increased levels of ET-1 on rat aortic rings, which resulted in an increase in O_2^- and provided evidence of reduced NO. This concept was further tested by Heimlich et al., (2015), examining effects of high salt diets on mice, which resulted in increases in renal ET-1 and NADPH oxidase activity causing an increase in ROS (Babior, 1999). Thus, a decrease in NO bioavailability contributes to increases in BP through a multifaceted system, although future research involving human tissue may help to pinpoint exact mechanisms.

Vascular dysfunction can also be attributed to increased vascular stiffness, which is a consequence of vascular remodeling (El Assar et al., 2013). Remodeling occurs through both structural and functional changes of the endothelium and smooth muscle cells, which cause disruption in communication between these cell types (El Assar et al., 2013). Arterial stiffness is an outcome of a decrease in arterial elasticity, facilitating an increase in BP (Zieman et al., 2005; El Assar et al., 2013). Arterial walls contain a balance of collagen and

elastin to maintain function, and over the course of the aging process elastin fibers undergo fragmentation and thinning, which results in a transfer of mechanical load and stress to collagen (100-1000 stiffer than elastin) (El Assar et al., 2013). Through this process, stiffening of the artery occurs, causing an overall increase in Q and TPR, which increases BP.

As noted above, numerous non-modifiable and modifiable factors increase an individual's lifetime risk of developing HTN. Non-modifiable risk factors are those that cannot be manipulated to reduce the development of HTN, and include: genetics/family history, age, sex, ethnicity, and environmental factors (Maranon & Reckelhoff, 2013; Franceschini et al., 2014; Hicken et al., 2014; Harvey et al., 2015). Unlike non-modifiable risk factors, potential modifiable factors can be manipulated in order to decrease HTN development and occurrence. Modifiable risk factors related to the development of HTN include: obesity, diabetes mellitus, and tobacco smoking (Padwal et al., 2001).

A gene carries specific information to form a trait, which is transferred from parents to children in the formation of that organism (Reece et al., 2013). Passing on these specific traits or conditions that determine an individual's genetic make-up (Reece et al., 2013). Abnormal BP control is a heritable trait that may be passed through generations with genetic contribution to HTN ranging from 30-50% (Franceschini et al., 2014). However, determining genes directly responsible for HTN development has been challenging with exact genes remaining elusive (Franceschini et al., 2014). Due to the complex nature of HTN, it is possible that there is interplay between other genetic factors like age, race

and sex that may provide possible explanations for HTN development (Franceschini et al., 2014).

Aging is a major non-modifiable risk factor in the development of HTN, and is associated with endothelial dysfunction, vascular remodeling, and increased vascular stiffness (Najjar et al., 2005; Harvey et al., 2015). Aging increases the likelihood of HTN at around age 45 years for men, and age 55 years for women (Statistics Canada, 2016b). In Canada, approximately 9% of men and 6% of women aged 35-44 years have HTN (Statistics Canada, 2016b). This increases to around 20% and 13% of men and women, respectively, at ages 45-54 years (Statistics Canada, 2016b). Prevalence of HTN becomes greater at age 75 years and older, with half of men (approximately 49%) and of women (approximately 55%) living with HTN (Statistics Canada, 2016b). The vascular changes associated with aging are thought to lead to chronic elevations of BP, including vascular remodeling, which occurs over the life span (El Assar et al., 2013). Neural regulation also declines as we age, as muscarinic receptor activity (discussed in Section 1.2.2, pg.12) is weakened resulting in a decrease in SNS and PNS regulation of the heart (e.g. SNS modulation in times of stress to cause a rise in HR and BP) (Lakatta, 2015). Consequently, there is an increased level of plasma E and NE thought to engage these receptors in older individuals compared to younger individuals, which when combined with the decrease in clearance of the hormones, results in an increase in BP (Manolis & Poulimenos, 2014; Lakatta, 2015).

Hypertension (HTN) development is different depending on the ethnicity of the individual (Hicken et al., 2014). For example, research has suggested African Americans are more likely to have HTN after age 45 years, be aware of their condition, and receive treatment, but are less likely to reach target BP values with treatment when compared to Caucasian Americans (Hertz et al., 2005; Howard et al., 2017). Possible physiological explanations have been explored, with some evidence suggesting that hypertensive African Americans have higher levels of ET-1 when compared to hypertensive Caucasian Americans (Ergul et al., 1996). Campia et al., (2004) highlighted that disparity in BP may be the result of increased receptor sensitivity to ET-1 in combination with higher plasma levels of ET-1 that may be creating elevations in BP. However, further study is needed to truly understand this HTN disparity, with future research focusing on a comparison of a broader range of ethnicities for a complete understanding.

Similarly, there are also differences that exist between men and women regarding the development of HTN (Maranon & Reckelhoff, 2013). It has been suggested that in young healthy women β-adrenergic mediated dilation is greater in comparison to men, which provides some level of protection against SNS over-activity and contributes to this group having lower resting BP (Kneale et al., 2000; Hart et al., 2012). Evidence indicates that this may be a reason why young women are less likely to be diagnosed with HTN when compared to young men of the same age (Hart et al., 2012). Specific mechanisms illuminating why β-adrenergic receptor sensitivity is greater in women is unclear, although there is work from animal models to support the notion that estrogen increases the

receptor sensitivity (Hart et al., 2012). The absence of this protective component has been observed in post-menopausal women, with reduced levels of circulating estrogen related to a decrease in β-adrenergic receptor sensitivity (Hart et al., 2012). In contrast, the hormone testosterone is also linked to differences in BP that may occur between sexes, potentially explaining why men are at a higher risk of developing HTN before the onset of menopause in women (where HTN appears equal for both men and women) (Kienitz & Quinkler, 2008; Zimmerman & Sullivan, 2013). For example, castration of spontaneously hypertensive male rats resulted in a decrease in BP and when these animal models were then given testosterone these observations become inversed (Kienitz & Quinkler, 2008). Testosterone is suggested to increase synthesis of NE, in which case may lead to an increase in SNS activity (Kienitz & Quinkler, 2008). However, research is inconclusive on the HTN disparity between the sexes based on testosterone levels, with evidence supporting reduced testosterone levels also associated with HTN development (Kienitz & Quinkler, 2008; Hart et al., 2012; Zimmerman & Sullivan, 2012). Future direction may include specialized treatment plans according to ethnicity and sex of an individual to promote effective treatment (Kienitz & Quinkler, 2008).

Unlike the previous factors, environmental elements are part of an individual's external living circumstances, but also contribute to HTN pathology to compound previously mentioned morphology. Air pollution, referred to as particulate matter (PM), has recently been studied, and related work provides evidence that air-pollutants effect HTN development (Cosselman et al., 2015).

Dvonch et al., (2009) examined the effects of ambient PM by daily BP measurements on 347 residents of Detroit, Michigan over a two-year period. Results of this study provided evidence that increased exposure to PM was associated with increased BP. Specifically, for every 10-μ/m^3increase in PM there was also an increase in SBP of approximately 3 mmHg. Brook et al., (2014) found similar results acutely, as adults exposed to 2-hour periods of PM, which caused increases of 3-4 mmHg SBP. Speculated biological explanations include SNS over activity, arterial vasoconstriction, and endothelial dysfunction (Franklin et al., 2015). Although exact details of these biological mechanisms remain elusive, the evidence provided suggests that air pollution is a major contributor to the current HTN crisis, and is affected by both acute and chronic exposure (Franklin et al. 2015).

With regards to obesity, a modifiable risk factor linked to HTN, higher levels of fat mass have been associated with higher levels of SBP and DBP (Leung et al., 2017; Nerenberg et al., 2018). In Canada, 30% of adults who were classified as overweight or obese were also classified as being hypertensive, compared to 12% of normal weight adults with HTN (Statistics Canada, 2015a). Research has indicated that obesity is linked to over activity of the SNS, and changes in renal Na+ and water retention (as discussed previously above) (Rahmouni, 2014). These changes have been seen in animal models as demonstrated by Armitage et al., (2012) by feeding a high fat diet to rabbits for a time period of 3 weeks. Rabbits who were fed this high fat diet gained 504 grams of excess fat over the 3-week test, which resulted in increased BP, HR, renal

sympathetic nerve activity, and impaired baroreflex function (Armitage et al., 2012). As with the Armitage et al., (2012) study, evidence has shown renal sympathetic activity to be increased with obesity, altering BP further through fluid and Na+ retention in the renal tubules (Rahmouni et al., 2014). Lohmeier et al., (2012) observed this phenomenon by baroreflex stimulation in dogs fed high fat diets. When the dogs gained 50% of their original weight during feeding, marked increases in BP, HR, MAP, and sodium retention were observed. However, when baroreceptor activation by electrical stimulation was initiated, this induced state of HTN disappeared, with reductions in plasma NE and reduced rates of sodium reabsorption by the renal tubules. With these results in mind, control of excess weight has been incorporated into current HTN guidelines (Leung et al., 2017; Nerenberg et al., 2018) as a method of decreasing chances of HTN development or reducing BP in hypertensive individuals (as discussed below in Section 1.2.4 Treatment, pg. 36). Excess weight is theoretically a modifiable risk factor as it can be commonly mitigated by proper diet and exercise to cause fat-mass reduction and an overall maintenance of more ideal body fat levels (McArdle et al., 2010). However, there are other factors that may prevent weight from being a completely modifiable factor as socioeconomic status may limit exercise and proper nutrition, or hormonal imbalances may create a level of difficulty the average person may not struggle with (Bhurosy & Jeewon, 2014; Mullur et al., 2014).

Diabetes is characterized by a malfunction in the action of insulin, the secretion of insulin, or both complications simultaneously, resulting in

hyperglycemia (American Diabetes Association, 2014). Approximately 90-95% of diabetes cases are classified as diabetes mellitus (also known as type 2 diabetes, or adult onset diabetes), which consists of decreased insulin sensitivity and a relative insulin deficiency (American Diabetes Association, 2014). Although direct causes of diabetes mellitus are unknown, increases of abdominal body fat are commonly seen in those with a diagnosis, and ultimately, also contribute to the development of HTN (American Diabetes Association, 2014). It is theorized that an increase in SNS activity is linked to a greater chance of developing diabetes mellitus and HTN, creating an overlap between diseases (Sowers, 2013). Oxidative stress and inflammation are increased with diabetes mellitus, and these occur concomitant to a decreased bioavailability of NO (Cheung & Li, 2012; Sowers, 2013). This is accomplished through increases in SNS activity, which causes increases in the RAAS system activity that is common in diabetics (Cheung & Li, 2012). Malfunction in the endothelium may be due to overstimulation of angiotensin II release, which in turn fosters ROS formation reducing the effectiveness and bioavailability of NO (Cheung & Li, 2012). This decreased bioavailability then causes a reduced ability for endothelial-mediated vascular relaxation in the arteries, attenuating the capabilities of the body for vasodilation, thus, causing arterial stiffness, and a chronically elevated BP (Cheung & Li, 2012; Sowers, 2013). This can be characterized by a narrowing of the blood vessels, which increases TPR and results in BP to be higher in diabetic individuals (Sowers, 2013). Insulin resistance seen in type 2 diabetics is thought

to increase the SNS, which leads to the increases in ROS and HTN (Cheung & Li, 2012).

Tobacco smoking has also been identified by the World Health Organization as a leading modifiable risk factor in developing HTN (WHO, 2018b). Smoking cigarettes increases arterial stiffness, thus increasing TPR and BP (Kim et al., 2005). It also affects the cardiovascular system by means of two toxic chemicals: nicotine, and carbon monoxide (Leone, 2015). Receptor binding of nicotine stimulates the SNS through release of E and NE, effectively raising HR and SBP (Leone, 2015). Nicotine also promotes endothelial dysfunction as it causes a reduced bioavailability of NO through increased oxidative stress (Leone, 2015). This reduction of NO reduces the endothelium's capability of vasodilation, and thus, contributes to an increase in BP (Leone, 2015). Carbon monoxide also contributes to increases in BP by causing hypoxia (Leone, 2015). Carbon monoxide is formed in the body when carbon binds to oxygen, and has the potential to then bind to hemoglobin (Leone, 2015). Once carbon monoxide is bound to hemoglobin, it forms carboxyhemoglobin reducing the efficiency of the blood to deliver oxygen to tissues (Leone, 2015). Hypoxia, in this case, causes an increase in HR and BP to adapt to this reduced efficiency in order to accommodate the reduced oxygen at the tissue.

1.2.4 Treatment of Hypertension

The goal of HTN treatment is to lower elevated BP to within clinical target ranges (Leung et al., 2017; Nerenberg et al., 2018). Although ever changing, it is generally recommended that OBP is controlled to below 140 mmHg SBP and 90

mmHg DBP, or ≤ 135 mmHg SBP and 85 mmHg DBP using AOBP or ambulatory devices (WHO, 2013; Leung et al., 2017; Nerenberg et al., 2018). The most recent AHA/ACC guidelines suggest a target for BP lowering to <130/80 mmHg, which was based on the success seen in the Systolic Blood Pressure Intervention Trial (SPRINT) study that incorporated targets of <120 mmHg (Ambrosius et al., 2014; Whelton et al., 2018). Currently, lifestyle modifications and pharmacotherapy are cornerstone treatments for HTN management.

The goal of lifestyle modifications is to recognize the condition(s) and manage all other identifiable risk factors for HTN (Weber et al., 2014). Treatment processes are usually a lifelong commitment, and termination of recommended lifestyle changes or pharmaceutical prescriptions may be life threatening (Weber et al., 2014). Endorsed lifestyle modifications include increasing physical activity, weight reduction, decreasing alcohol consumption, following the Dietary Approaches to Stopping HTN (DASH) diet, and an overall reduction of daily stress (Leung et al., 2017; Nerenberg et al., 2018). With regards to physical activity, the accumulation of 30-60 minutes of moderate intensity dynamic exercise (e.g., walking, running, cycling, swimming) 4-7 days per week in combination with daily activities is recommended to reduce BP (Leung et al., 2017; Nerenberg et al., 2018). These guidelines are supported by complementary guidelines around the world (Mancia et al., 2013, Weber et al., 2014; Pescatello et al., 2015; Leung et al., 2017; Nerenberg et al., 2018; Whelton et al., 2018). The 2017 AHA/ACC guidelines stress the importance of also

incorporating dynamic resistance exercise and isometric resistance exercise into exercise training programs for optimal BP control (Whelton et al., 2018). Dynamic resistance exercise recommendations include 90-150 minutes of training at 50%-80% of an individual's 1 repetition maximum, with 3 sets per exercise, 10 repetitions per set, for at least 6 exercises total (Whelton et al., 2018). Decreases seen in hypertensives following said dynamic resistance training recommendations result in a BP reduction of approximately 4 mmHg (Whelton et al., 2018). Additionally, isometric resistance training, which has recently been added to the recommendations, employs an exercise program using a handgrip dynamometer (discussed further in Section 1.3, pg. 44), completing 4, 2-minute contractions at 30%-40% of an individual's maximum voluntary contraction (MVC), separated by 1-minute rest periods (Whelton et al., 2018). Training should occur at least 3 times per week (Whelton et al., 2018). With regard to diet, the DASH diet is a main recommendation for individuals living with HTN (Sacks et al., 2001). The DASH diet puts emphasis on fruits, vegetables, low fat dairy products, whole grains, poultry, fish, and nuts with small amounts of red meats, sweets, and sugary snacks (Sacks et al., 2001).

Although these methods are effective, unfortunately many Canadians are not meeting daily requirements for physical activity or diet (Statistics Canada, 2015b). This is exemplified by the fact that most Canadian's waking hours are sedentary 68% for men and 69% for women), and only 25% of the population are accumulating 150 minutes of moderate to vigorous aerobic physical activity per week as per the guidelines (Colley et al., 2018). Moreover, less than 40% of

Canadians aged 12 years or older eat fruits or vegetables 5 or more times per day (Statistics Canada, 2015b).

When lifestyle modifications are insufficient in lowering BP to within the clinical target, pharmacological treatments are then prescribed along with lifestyle-related treatments (Weber et al., 2014). Common medications prescribed include angiotensin enzyme inhibitors, which reduce the conversion of angiotensin I to angiotensin II, and angiotensin receptor blockers, which bind to the receptor to prevent vasoconstriction by angiotensin II. Other medications include thiazide and thiazide-like diuretics, which increase sodium excretion by the kidneys; $Ca^{2}+$ channel blockers, which block inward flow of $Ca^{2}+$ ions through the L channels of the arterial smooth muscle cells, lowering TPR and BP; and β-blockers which prevent E from increasing HR and BP (Weber et al., 2014).

1.2.5 Exercise Training

Effects of Acute Aerobic Exercise on Blood Pressure

Acute exercise has the potential to lower resting BP levels post-exercise, an occurrence named post-exercise hypotension (PEH) (Halliwill et al., 2014). The effect has been observed for up to 22 hours after the completion of a bout of aerobic exercise (Chen & Bonham, 2010; Halliwill et al., 2014); individuals with higher pre-exercise levels experience the largest reductions (Syme et al., 2006). In general, average reductions in BP following a bout of aerobic exercise for normotensives and hypertensives are 8/9 mmHg and 10/7 mmHg SBP and DBP, respectively (MacDonald, 2002).

Although most PEH studies to date have involved resting BP as a primary outcome, work by Ciolac et al., (2008) in post-menopausal women provided evidence of 24-hour BP lowering after an acute bout of aerobic exercise. Specifically, post-bout reductions in 24-hour SBP, 24-hour DBP, daytime SBP, daytime DBP, nighttime SBP, and nighttime DBP were observed. Of interest, it has been suggested that PEH may be a useful predictor for how an individual will respond to chronic exercise training with BP-lowering (Ciolac et al., 2008). Kiviniemi et al., (2015) demonstrated this concept by an acute aerobic exercise test followed by a training protocol. Pre-training PEH-related decreases in SBP was related to post-training reductions in resting SBP (Kiviniemi et al., 2015).

Although the potential mechanisms are elusive, it has been proposed that the phenomenon can be explained by two different mechanisms. The first, baroreceptor resetting (in which GABAergic interneurons exert less inhibitory effects on barosensitive neurons, leading to a decrease in sympathetic outflow) or the second, a sustained level of post-exercise vasodilation caused by histamine receptor activation (Chen & Bonham, 2010; Halliwill et al., 2014).

Effects of Chronic Aerobic Exercise on Blood Pressure

Chronic effects of aerobic exercise have been extensively researched, with concrete evidence for reductions in resting BP. Generally, research has shown that aerobic exercise training interventions elicit average BP reductions of approximately 2/2 mmHg and 7/5 mmHg for normotensives and hypertensives, respectively (Cornelissen et al., 2013). Extensive research has been completed to support the efficacy of aerobic training in lowering resting BP despite the

multitude of modalities (walking, running, cycling, organized sport), intensities (30-90% of maximal oxygen reserve), durations (30-60 minutes), and frequencies (1-7 days per week) implemented (Pescatello et al., 2004; Lamina, 2010; Dimeo et al., 2012; Krustrup et al., 2013; Arca et al., 2014; Börjesson et al., 2016).

The mechanisms responsible for BP reductions seen with chronic aerobic exercise participation remain inconclusive, although it is speculated several components are involved (e.g. neural, hormonal, local) and that reductions in BP due to aerobic training can be attributed to changes to TPR rather than Q (Pescatello et al., 2005). This also coincides with the notion that a decrease in SNS activity due to aerobic training will increase vasodilation, effectively decreasing TPR and BP (Pescatello et al., 2005). Aerobic exercise performed for prolonged periods may reduce BP locally via reductions in ET-1 and ROS, while increasing bioavailability of NO, which has recently been shown in animal models during an 8-week training program (Maeda et al., 2001; Pescatello et al., 2004; Braga et al., 2015; Wilson et al., 2016). Exercise induced anatomical adaptations of the heart may also have an influence on BP, with aging endurance athletes (65 years or older) having lower end systolic/diastolic volumes in both the left ventricle and right ventricle in combination with similar increases in left ventricle wall thickness seen in younger endurance athletes (Whyte et al., 2004; Wilson et al., 2016).

There is a growing body of research examining the effects of chronic aerobic training on ambulatory BP (Cardoso et al., 2010). Current meta-analysis suggests an average reduction in daytime BP of approximately 3/3 mmHg and 3-

12/3-7 mmHg for normotensives and hypertensives, respectively (Gayda et al., 2012; Cornelissen et al., 2013). Dimeo et al., (2012) demonstrated the effects of an 8-week treadmill exercise program on 50 participants with resistant HTN, where the use of 2 or more antihypertensive drugs were ineffective to lowering BP alone. Completion of the protocol resulted in a decrease in daytime ambulatory SBP and DBP.

Effects of Acute Dynamic Resistance Exercise on Blood Pressure

An acute bout of dynamic resistance exercise using large muscle groups to lift weights through a series of dynamic movements produces immediate increases in both SBP and DBP up to 400 mmHg and 200 mmHg, respectively (MacDougall et al., 1985; Mayo et al., 1999). Intramuscular pressure created by compression of the vasculature causes a drastic increase in TPR, which increases in BP (Mayo et al., 1999).

Sympathetic nervous system (SNS) activity is also enhanced, increasing NE secretion to augment HR and BP and provide adequate amounts of oxygenated blood to working tissues (Mayo et al., 1999; Kraemer & Ratamess, 2005). However, the intensity of the working muscle activated and the amount of muscle mass that is activated proportionally determines the increase in BP to the acute bout of dynamic resistance exercise (Mayo et al., 1999). BP is also linked to the phase of the lift, where the onset of the lifting phase will increase BP to maximal levels, followed by a decrease in BP once the lift is completed, and an increased BP level during the lowering phase of a lift (MacDonald, 2002).

Similar to acute aerobic exercise, evidence suggests that PEH occurs

after an acute bout of dynamic resistance exercise, with limited research involving ambulatory BP methods (Pescatello et al., 2004; Cardoso et al., 2010). Melo et al., (2006) conducted experiments using a low-intensity strength training protocol on medicated hypertensive women aged 41-50 years (n= 11, resting BP = <160 mmHg/ 105 mmHg). Participants underwent low intensity resistance exercise performed in a random order with an interval of at least 7 days. Ambulatory BP was taken, with awake SBP, and DBP significantly lower in exercise groups compared to control groups, with 21-hour readings yielding a drop from approximately 128 mmHg/ 80 mmHg to 123 mmHg/76 mmHg, respectively. Simão et al., (2005) also examined hypotensive effects after acute resistance exercise with varying intensity, varying volume, and alternate training methods. After each training session, participants were outfitted with ambulatory BP monitors to determine post-exercise BP. The major finding of the study was PEH response duration may be related to resistance exercise training volume at high intensities, with PEH occurring for 60 minutes after 6 exercises and 50 minutes after 5 exercises. Recent meta-analysis research indicates PEH occurs 60-90 minutes post-exercise, with BP reductions proportional to pre-exercise values, and larger muscle groups eliciting a greater PEH response (Casonatto et al., 2016). These findings do coincide with previous research; therefore, continual study of this phenomenon must be completed in order to fully understand the mechanisms behind PEH following a bout of dynamic resistance exercise (Simão et al., 2005; Melo et al., 2006).

Effects of Chronic Dynamic Resistance Exercise on Blood Pressure

The literature regarding dynamic resistance training on BP is not as extensive as it is with aerobic training (Cardoso et al., 2010). A meta-analysis exploring randomized controlled trials of dynamic resistance training lasting at least 4 weeks facilitated SBP and DBP reductions of 4 mmHg in normotensives and 4/2 mmHg in hypertensives (Cornelissen et al., 2011). The latter results (hypertensives) findings were not statistically significant, but this may be due to the small body of work completed in the field (Cornelissen et al., 2011). However, more recent research conducted by Mota et al., (2013) investigated the effects of prolonged training on older adult, hypertensive women (n=64). Exercise sessions were conducted three times per week for 16 weeks with increasing load (Month 1: light intensity; Month 2: 60% 1RM; Month 3: 70% 1RM; and Month 4: 80% 1 RM). Results showed an approximate difference in SBP of 14 mmHg and DBP of 4 mmHg. Moreira et al., (2016) then completed a study of similar design on 20 medicated hypertensive women over the age of 60 years with 12 weeks of incremental dynamic resistance training. As with previous work, higher baseline BP was related to high acute BP responses, which then manifested as a greater BP lowering response to prolonged resistance training. Results of these studies indicate that PEH response seen acutely is related to long term effects of resistance training, similar to aerobic exercise (Moreira et al., 2016). However, whether the mechanisms are the same is still unclear.

Currently, there is limited research with regards to the ambulatory BP-lowering effects of dynamic resistance training, but the data to date suggests a

lack of effect (Blumenthal et al.,1991; Pescatello et al., 2004; Cardoso et al., 2010).

1.3 Isometric Resistance Exercise

A more novel intervention in the field of HTN management is isometric resistance training, in particular isometric handgrip (IHG) training. IHG training has emerged as a promising strategy that may be especially effective for reducing BP in individuals who have difficulty managing their HTN (Brook et al., 2013; McGowan et al., 2017). A typical IHG protocol involves the use of a computerized handgrip dynamometer with participants performing 4, 2-minute sustained squeezes (isometric contractions), each separated by 1-minute rest intervals (Badrov et al., 2013). The 2-minute isometric contractions are performed at 30% of an individual's MVC and most often completed bilaterally (Brook et al., 2013; McGowan et al., 2017). The individual is usually guided through the described process via onscreen instructions and prompts displayed on the computerized handgrip dynamometer. IHG training is typically performed 3-5 times per week for 8-10 weeks (Brook et al., 2013; Millar et al., 2014; Inder et al., 2016; McGowan et al., 2017). Reductions in resting BP due to IHG training have been noted in a wide array of individuals ranging from young adults (18-30 years) to older adults ($\geq$60 years), including those with and without HTN (McGowan et al., 2007; Badrov et al., 2013; Millar et al., 2014; Inder et al., 2016). After years of accumulating evidence supporting the effectiveness of IHG training in BP control, the ACC/AHA supports its use as a treatment for HTN management, and cites it as a "Best Proven Nonpharmacological Interventions

for Prevention and Treatment of Hypertension" in their most recent guidelines (Whelton et al., 2018). The CHEP are less specific in their recommendation, and acknowledge a lack of adverse effects with handgrip training (Brook et al., 2013; Leung et al., 2017; Nerenberg et al., 2018; Whelton et al., 2018). This type of treatment may also bridge the gap for individuals who are incapable of participating in or sustaining aerobic or dynamic resistance exercise-based treatments, and may be a remedy for the growing burden of HTN in low-middle income countries (Carlson et al., 2014).

Effects of Acute Isometric Handgrip on Blood Pressure

During an isometric muscle contraction, the underlying vasculature becomes compressed and occlusion of blood flow occurs (Smith et al., 2005). This reduced blood flow causes an accumulation of local metabolites (lactate, adenosine triphosphate, K+, and H+), which activates a mechanism known as the exercise pressor reflex (EPR) (Smith et al., 2005). SNS activity is then increased by the EPR relaying afferent signals to the CC, thus increasing HR and ultimately blood flow to the working tissues (Smith et al., 2005). Although definitive mechanisms as to how IHG affects BP remain unclear, the BP lowering effects have been documented through many studies. Current data supports only modest and transient increases in SBP and DBP (Δ 12-38/7-23 mmHg) during the contraction phase of the traditional IHG protocol (4, 2-minute isometric contractions each separated by 1-minute rest intervals) for most people studied thus far, even in those with HTN (Wiley et al., 1992; McGowan et al., 2006; Millar

et al., 2009; Araujo et al., 2011; Millar et al., 2014; McGowan et al., 2017; Smart et al., 2017).

The effects of an acute bout of IHG exercise on PEH are under-investigated. Millar et al., (2009) and Araujo et al., (2011) had both observed PEH following 4, 2-minute sustained isometric contractions at 30% of the participant's MVC with 1-minute rest periods in between each contraction, with PEH of -3 mmHg SBP in older normotensive individuals and -12 mmHg SBP/-11 mmHg DBP in young normotensives. In contrast, Bartol et al., (2012) did not observe PEH following an acute IHG bout in a population of well controlled, medicated hypertensives, either at baseline or following an additional 8 weeks of 3X/week IHG training. However, results of this study may have been impacted by the medication regimens of the participants. Similarly, Olher et al., (2013) did not find any instance of PEH after acute bouts of IHG at any intensity in a similar cohort of individuals medicated for HTN. Ash et al., (2017) investigated the antihypertensive effects of both acute aerobic sessions and acute IHG sessions in middle aged adults with prehypertension and obesity, and only observed PEH following the aerobic exercise bout. However, it is important to note that the amount of time engaged in aerobic exercise was far greater to be appropriately compared, and the IHG group was under-powered statistically. Further investigation is needed to fully understand the interaction between varying populations, differing IHG methods, and intensities with regards to PEH.

Effects of Chronic Isometric Handgrip on Blood Pressure

The most current meta-analysis of randomized trials cites average post-training BP reductions of 5/4 mmHg, with greater reductions seen in individuals with HTN (Inder et al., 2016). However, there is evidence that inter-individual differences may occur with this type of training. Work from Millar et al., (2008) suggested post-menopausal women experienced greater post-training BP reductions in comparison to men of a similar age. In general, the small overall number of women that have participated in IHG training trials to date make the effects of sex difficult to ascertain (McGowan et al., 2017). With respect to age, the most recent meta-analyses data provided evidence that adults > 45 years of age experience larger reductions in MAP than those < 45 years of age (Inder et al., 2016). Individuals with high pre-training SBP reactivity to math and isometric contraction stress tasks also appear highly responsive to IHG training (McGowan et al., 2017; Somani et al., 2017).

There is a lack of research regarding duration, intensity, and volume of training (Lawrence et al., 2015), yet training for ≥ 8 weeks appears to elicit larger reductions in SBP (7 mmHg vs. 3 mmHg), although there is no difference seen in DBP when making this comparison (Inder et al., 2016). In Wiley et al., (1992), the first of two studies consisted of testing IHG on subjects with high-normal resting DBP, performing the isometric handgrip contractions for 2-minutes at 30% of an MVC, with a 3-minute rest between each set of 2-minute contractions, 3 days per week for 8 weeks. Training resulted in a decline of both SBP and DBP of approximately 13 mmHg and 15 mmHg, respectively. In the second study,

borderline hypertensive participants were chosen to complete 4, 45 second contractions at 50% MVC with 1-minute rest intervals between contractions, 5 days per week for 5 weeks. Training resulted in significant reductions in SBP and DBP pressure of 10 mmHg and 9 mmHg, respectively. Badrov et al., (2013) investigated the effects of IHG volume on BP-lowering effectiveness in normotensive women. Participants were either categorized into IHG3 or IHG5, which consisted of training 4, 2-minute contractions at 30% MVC for either 3 times per week or 5 times per week for 8 weeks. Both groups had similar reductions in SBP (6 mmHg), yet the IHG5 group achieved significant BP reductions after 4 weeks of training, while the IHG3 group only showed these reductions after 8 weeks of training.

Although only IHG training appears in current BP-lowering guidelines (Leung et al., 2017; Nerenberg et al., 2018; Whelton et al., 2018), there is evidence to suggest that isometric leg (IL) training elicits similar BP-lowering benefits, although much of the work has been conducted in normotensive populations. Previous experimentation has involved a general practice of double leg contractions based on 20-50% of the individuals MVC, consisting of 4, 2-minute isometric contractions separated by 3-minute rest periods, taking place 3 times per week for up to 4-8 weeks (Gill et al., 2015). Devereux et al., (2010) demonstrated that 4 weeks of IL training reduced SBP and DBP by 5 mmHg and 3 mmHg, respectively, in a cohort of young healthy adults.

With respect to investigations involving exercise intensity and BP-lowering effect, Wiles et al., (2010) investigated intensity levels of IL training on BP.

Participants (n=33) were divided into control, high intensity (20% MVC), or low intensity (10% MVC) grouping, which required IL training (4, 2-minute isometric contractions separated by 1-minute recovery) 3 times per week for 8 weeks. Changes seen in resting BP were significant for high intensity and for low intensity, systolic, diastolic, and MAP. This demonstrated that lowering BP can be achieved at a wide range of intensities when using IL protocols. Baross et al., (2012) then replicated this study using 14% MVC for the high intensity group and 8% MVC for the low intensity group. Significant changes in BP (MAP and SBP) were only seen in the high intensity group after training.

The mechanisms responsible for the demonstrated reductions in BP following IHG training remain unclear. As noted previously, HTN is associated with dysfunctional vagal HR modulation, increased SNS activity and vascular dysfunction (Anderson et al., 1989; Singh et al., 1998; Faulx et al., 2003). Work to date supports improved vagal control of HR (Taylor et al., 2003; Millar et al., 2014), reduced sympathetic activity (Taylor et al., 2003) augmented arterial compliance and vascular function (McGowan et al., 2006, McGowan et al., 2007; Badrov et al., 2013; Millar et al., 2014), enhanced oxidative capacity (Peters, et al., 2006), and reduced Q (Wiles et al., 2017) as potential contributors to the BP-lowering effects of IHG training.

1.4 Alternative Devices: Stress Ball

Although the benefits of IHG training have been documented as described above, the high cost of the computerized IHG dynamometer employed (> $699 CAD; Zona Health, 2018) and lack of insurance coverage for the device creates

an economic barrier to its implementation (McGowan et al., 2017). Previous studies have identified the importance of developing cost-effective alternative devices or techniques as a method of broadening isometric resistance training as a viable treatment option for individuals with HTN (Millar et al., 2008; Zhang et al., 2014; Wiles et al., 2017). The WHO has also endorsed the implementation of cost effective, efficient, and innovative ways to reduce BP (WHO, 2017).

Early evidence suggests that alternative and affordable devices/techniques elicit short-term training-induced reductions in BP. With respect to IHG training, Millar et al., (2008) provided support for the BP-lowering effects of a spring-loaded IHG device in normotensive older adults. Participants who trained 3 times per week for 8 weeks at an intensity ranging from 15 to 30 pounds of force (depending on their baseline maximum force or MVC), experienced post-training SBP and DBP reductions of 10 mmHg and 2 mmHg, yet no changes were observed in the control group. This study provided the first evidence to suggest IHG training with a cost-effective device can elicit the same results. However, it is unclear if these results are generalizable to younger normotensive or older hypertensive cohorts, or if they can be replicated using other low-cost devices.

Similarly, Wiles et al., (2017) investigated cost effective methods of IL by the effects of a 3 times per week wall squat (4, 2-minute bouts at 95% of $HR_{peak,}$ with 2-minute rest between bouts) 4 week training program on resting BP in young, normotensive men. Post-training reductions in SBP (4 mmHg), DBP (3mmHg), and MAP (3 mmHg) were observed. Although this method meets a

cost-effective model for isometric training, it does not meet feasibility due to the required lower limb strength that is necessary for participation. Thus cost-effective, widely available options must continually be explored to find the best option for isometric training.

An alternative and even less expensive device than the spring-loaded device previously investigated (Millar et al., 2008), one not reliant on calibration equipment to regulate force, and one that can be performed by individuals with mobility issues, balance issues, or barriers that may prevent exercise involving lower extremities is the widely known “stress ball”. Recent work by Morrin et al., (2018) lay a foundation for designing effective IHG protocols on non-computerized, non-spring-loaded devices. Using a pre-HTN and HTN cohort, it was demonstrated that a perceived exertion (CR-10) of 6 during a 2-minute IHG contraction is equivalent to approximately 30% MVC (Morrin et al., 2018). To date, no study has investigated the acute (during a bout) or chronic (training) effects of IHG on BP or other indices of cardiovascular and psychophysical function when using a stress ball.

1.5 Summary

HTN is the leading cause of CVD-related mortality, making it a substantial contributor to global disease burden (WHO, 2017). With the number of CVD-related deaths increasing each year (WHO, 2017), effective BP control is essential, and a critical public health concern. The prevention and successful treatment of HTN is now a global health priority of the WHO (WHO, 2013). Current HTN treatment options include: reduction in excess body fat, cessation of

smoking, changes in diet (DASH diet), increases in physical exercise (following guideline recommendations), and pharmacotherapy (Nerenberg et al., 2018; Whelton et al., 2018).

Despite these published widespread recommendations, successful BP control is suboptimal, creating a need for new, innovative, time efficient, and cost-effective methods to reduce HTN (Newson & Kemps, 2007; WHO, 2017). IHG training is one such method, and has been recently endorsed by governing bodies for BP management (Nerenberg et al., 2018; Whelton et al., 2018). However, most isometric resistance training protocols present barriers limiting their use – whether it be expensive hand or leg dynamometer devices, difficult to calibrate spring-loaded IHG devices, or challenging wall squats. As such, long-term application of isometric resistance training as a BP-lowering treatment is unlikely for many individuals in North America and worldwide (Millar et al., 2011; Zona Health, 2018). As IHG training, and not IL training, is the endorsed method of training, exploring inexpensive and widely available IHG alternatives, such as the “stress ball” should be a priority. The enhanced feasibility, low maintenance, and inexpensive nature (approximately $4 CAD) of the stress ball aligns with the global (WHO, 2017) emphasis on reducing barriers to effective BP management.

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Chapter 2:
Getting the Best GRIP on Blood Pressure Control: Are Stress Balls and Computerized Handgrips Equally Effective?

2.1 Introduction

Cardiovascular disease (CVD) is the number one cause of death globally (WHO, 2017). In 2016, over 17 million or 31% of all global deaths were attributed to CVD (WHO, 2017). Hypertension (HTN; traditionally defined as resting blood pressure (BP) ≥140/90 mmHg; Gee et al., 2014; Nerenberg et al., 2018; Whelton et al., 2018; Williams et al., 2018) is the leading cause of CVD and CVD-related mortality, and the number one modifiable risk factor (Ezzati et al., 2002; Daneai et al., 2011; Joffres et al., 2013; Benjamin et al., 2017). Already affecting more than 1 billion people worldwide (Fisher & Curfman, 2018), the World Health Organization (WHO) has identified HTN as a global epidemic (WHO, 2013).

Cornerstone recommendations for the prevention, treatment and management of HTN include a reduction in alcohol consumption, cessation of tobacco smoking, maintenance of a healthy body weight, improvements in diet and increases in physical exercise (e.g., aerobic exercise together with dynamic resistance training), in addition to routine activities of daily living (Nerenberg et al., 2018; Whelton et al., 2018). When lifestyle modifications alone do not successfully control BP to within clinical target ranges (Eckel et al., 2014), pharmacotherapy is used concomitantly (Owen et al., 2010; Leung et al., 2017; Nerenberg et al., 2018; Whelton et al., 2018). Despite these intervention strategies, less than 50% of those with HTN have their condition controlled to target levels (Go et al., 2013). This may be attributable to many factors, such as non-adherence to medication, diet and/or physical activity regimens, and the cost of treatment (Brook et al., 2013; McGowan et al., 2017). Therefore, it is crucial to

develop complementary and cost-effective strategies that can be used alone or in conjunction with traditional BP-lowering interventions to better control BP (WHO, 2017).

Accordingly, alternative strategies have been investigated over the years with varying degrees of success (e.g., meditation, biofeedback, device-guided breathing), including isometric handgrip (IHG) training (Brook et al., 2013; McGowan et al., 2017). After decades of accumulating proof-of-concept evidence, the AHA/ACC now endorses IHG training as a treatment for HTN management, citing it as a “Best Proven Nonpharmacological Interventions for the Prevention and Treatment of Hypertension” in their most recent guidelines (Brook et al., 2013; Whelton et al., 2018). Typically, an IHG protocol involves the use of a computerized handgrip dynamometer with participants performing 4, 2-minute sustained squeezes (isometric contractions), each separated by 1-minute rest intervals (Badrov et al., 2013), at 30% of an individual’s maximum voluntary contraction (MVC) performed 3-5 times per week for 8-10 weeks (Brook et al., 2013; Millar et al., 2014; Inder et al., 2016; McGowan et al., 2017). However, there is concern over the accessible and economic feasibility of using such devices for widespread implementation.

The high cost of the computerized IHG dynamometer (> $600 CAD; Zona Health, 2018) and lack of insurance coverage for the device creates an economic barrier to its widespread uptake and implementation (Millar et al., 2008; Zhang et al., 2014; McGowan et al., 2017; WHO, 2017). This notion of using an alternative and affordable handgrip device has already been supported in the literature as

an approach to elicit short-term training-induced reductions in BP for normotensive older adults (Millar et al., 2008). Using a spring-loaded IHG device, participants completed an 8 week, 3 times weekly, IHG training program, or were part of a non-exercising control group. Participants randomized to the IHG group trained at an intensity ranging from 15 to 30 pounds of force, depending on their baseline maximum force or MVC. Pre-post reductions of 10 mmHg for systolic BP and 3 mmHg for diastolic BP were observed with training, yet no change was observed in the control group.

An alternative and even less expensive device than the spring-loaded dynamometer previously investigated (Millar et al., 2008), one not reliant on calibration equipment to regulate force, and one that can be performed by individuals with mobility issues, balance issues, or barriers that may prevent exercise involving lower extremities, is the widely known “stress ball”. Recent work by Morrin et al., (2018) lay a foundation for designing effective IHG protocols with alternative IHG devices. Using a pre-HTN and HTN cohort, it was demonstrated that a rating of perceived exertion (CR-10; RPE) of 6 during a 2-minute IHG contraction is equivalent to 30% MVC (Morrin et al., 2018). To date, no study has investigated the acute (during a bout) or chronic (training) effects of IHG on BP or other indices of cardiovascular and psychophysical function when employed using a stress ball.

Before a long-term training investigation can be undertaken, it is important to first examine and compare the acute stimuli of the inflatable stress ball with the

computerized device, including cardiovascular (BP and heart rate, HR), and RPE (similar to Morrin et al., 2018) responses.

2.2 Purposes and Hypotheses

The primary objective of the present investigation was to test the hypothesis that an acute bout of IHG utilizing an inexpensive, readily available inflatable stress ball would elicit a similar cardiovascular response (e.g., elevations in BP and HR) as the traditional computerized dynamometer device. In addition, it was anticipated that an acute bout of IHG would elicit a similar RPE of approximately 6 using both devices.

2.3 Clinical Significance

The current study extends the body of IHG training work and provides a base for future training studies designed to investigate the effects of less expensive devices on BP-reduction. The demonstration of similar cardiovascular and RPE responses to a bout of IHG using a computerized device (Zona Health, 2018) and an inexpensive inflatable stress ball (approximately $4 CAD) suggests that IHG training performed using the latter may have similar BP-lowering benefit. Further, gaining a greater understanding of the subjective RPE will address a gap exposed by Morrin et al. (2018) and generate knowledge that will inform programing decisions as to the feasibility of device as a standard of care treatment. Thus, this project lays the foundation for future studies to test efficacy and outcome benefit, further promoting IHG as a treatment option for BP management. Importantly, this work aligns with the WHO's request for valid prevention strategies that are equally cost-effective.

2.4 Methods

2.4.1 Study Participants

Participants (healthy adults, ≥ 18 years old, resting BP <135/85 mmHg, no overt disease, not taking prescription medication with the exception of birth control pills, over the counter medications (e.g., Tylenol, Benedryl) from within southwestern Ontario were recruited (Appendix A). All participants provided written and informed consent (Appendix B), and all procedures were cleared by the University of Windsor's Research Ethics Board.

2.4.2 Study Design

Following consent and determination of eligibility, participants completed a familiarization and testing session. Each of these sessions involved the measurement of HR and BP while performing a bout of IHG on i) a computerized IHG device (Zona Series 2, Zona Health, Boise, ID, USA, Appendix C) and, ii) a store-bought inflatable ball (Part Number 020500, AllBall, Sportime, Thailand. www.Amazon.com, Appendix D). The order of the two IHG methods (computerized IHG device and inflatable ball) were randomized for each participant with a 30-minute stabilization period between each bout. Total time to complete the collective procedures was approximately 3 hours and included 2 points of contact.

Visit 1: Eligibility and Familiarization (approximately 1 hour)

Following informed consent, initially eligible participants completed the Physical Activity and Readiness Questionnaire plus (PAR-Q+; Appendix E) and a medical questionnaire (Appendix F) with the intent to screen for any ailments that

may exclude them from participating. Additionally, resting BP was measured after 10 minutes of seated rest to ensure inclusion BP criterion was met (<135/85 mmHg) according to standard protocol (Dinamap Carescape v100, Critikon 23-33cm cuff, Tampa, Florida, USA; see Appendix G). Four measurements were acquired, with 2-minute rest periods between each measurement, and the last 3 BP values averaged. Participants meeting all eligibility criteria proceeded to protocol familiarization.

During the familiarization session, participants practiced the testing day procedures. The session began with determination of maximal voluntary contraction (MVC) on each device. The MVC for the computerized device (Series 2, Zona Health, Boise, ID, USA, see Appendix C) was automatically calculated from internal linear load cells, using either the right or left hand (depending on randomization). MVC for the inflatable stress ball (Part Number 020500, AllBall, Sportime, Thailand. www.Amazon.com, see Appendix D) was calculated using a digital air pressure gauge (Fox 40 International, 340 Grays Road, Hamilton, Ontario, Canada, 2016, see Appendix H). Then respective 30% MVC were calculated; for the computerized IHG device this calculation was done automatically, and for the inflatable stress ball the following equation was used:

Equation 1: S= Max PSI x 0.30;

where S represents the 30% value, and Max PSI is the maximum air displaced; the value displayed on the air gauge.

Once completed, the participant performed a 2-minute IHG bout at 30% MVC using their right hand. After the bout was finished, the participant was given

the chance to review the CR-10 scale (Appendix I) and have their BP measured as per testing day procedures. After a 1-to-2-minute rest period, this process was completed on the left hand and the alternative device was used for the second bout to ensure minimal fatigue experienced during this familiarization session.

Visit 2: Testing Day (approximately 1.5 hours)

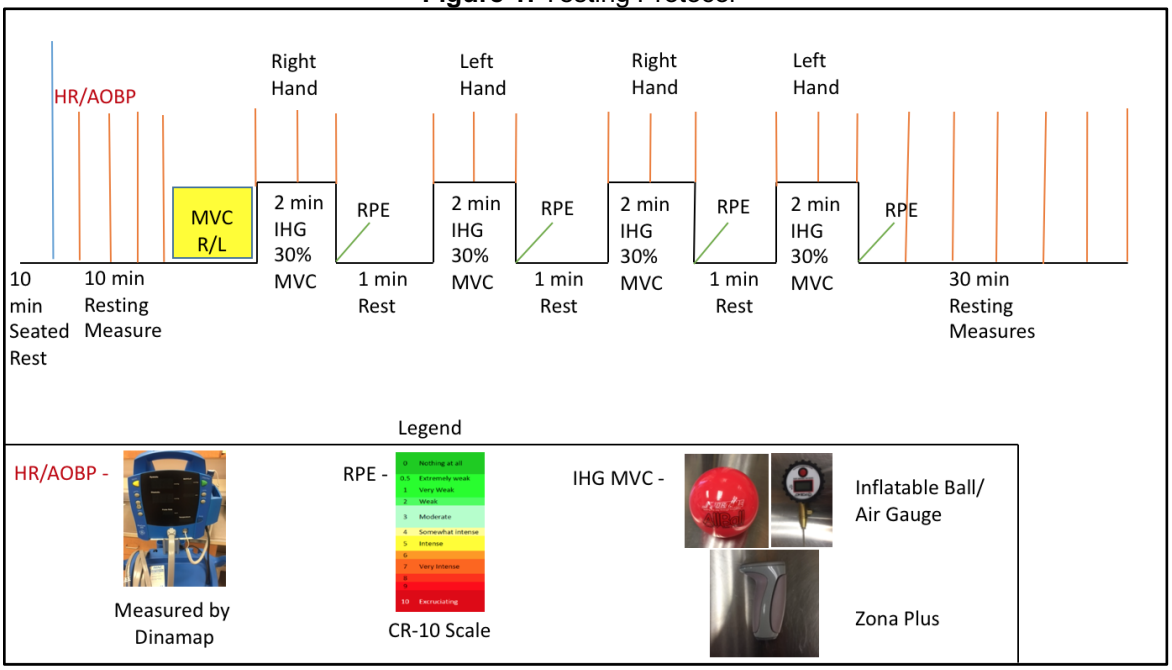
After confirmation of ongoing consent (Appendix B), and at least 24 hours after the familiarization session, a single testing session occurred. All participants were tested in the morning to control for the effects of circadian rhythm on BP, and in a temperature-controlled room. Participants refrained from vigorous physical activity over the previous 24 hours, were tested 2 hours postprandial (i.e. 2 hours after eating) and at least 12 hours post-caffeine consumption. To minimize the effects of a full bladder on BP, participants were asked to void his or her bladder prior to testing.

Participants were seated for the duration of the testing period, with both their right and left forearms resting on a table in front of them at an approximate 90-degree angle. Participants were outfitted with the necessary equipment to assess BP and HR (Dinamap Carescape v100, Critikon 23-33cm cuff, Tampa, Florida, USA, see Appendix G). Resting BP was measured following 10 minutes of seated rest as per the protocol described above. The protocols were separated by a 30-minute rest period (minimum) or until the participant's BP had returned to near resting values.

In both conditions, the IHG bout consisted of 4, 2-minute bilateral (right and left hand) contractions at 30% MVC each separated by a 1-minute rest period,

where BP and HR are measured every minute and RPE was recorded after each contraction (see Figure 1).

Figure 1: Testing Protocol



Note: Light blue line is the end of seated rest, each orange line is a blood pressure (BP) and heart rate (HR) measurement completed with automated office blood pressure measurements (AOBP) via Dinamap. Protocol began with a maximum voluntary contraction (MVC), where 30% was calculated for both the Right (R) and Left (L) hands. After the participant engaged in 4, 2-minute bilateral isometric handgrip (IHG) contractions, where a subjective rating of perceived exertion (RPE) was recorded after each contraction. After, there is a 30-minute stabilization period where BP and HR were measured. Once 30 minutes was complete the protocol began at the yellow MVC square again with the second device.

2.4.3 Statistical Analysis

Two-way repeated measures ANCOVA (RMANCOVA) were used to determine the effects of IHG device (independent variables: computerized or inflatable stress ball) on BP (SBP, DBP), HR and CR-10 scores (dependent variables). To determine specific differences between means, Boneferroni post-hoc test(s) were employed where appropriate.

All data were analyzed using IBM SPSS Statistics 23 software (SPSS Inc., Chicago, Illinois, USA) and statistical significance was determined at $p \leq 0.05$.

Data is presented as mean and standard deviation ($\bar{x}$ ± SD). Assumptions of sphericity were met for all conditions, with the exception of DBP, where the assumption for the two-way interaction between device and time was violated ($x^2(2) = 11.31$, $p = 0.05$). Thus, Greenhouse-Gieser was employed (€= 0.70).

2.5 Results

Twenty participants met the eligibility criteria and were enrolled in the study (see Table 1), satisfying the minimum requirements for adequate power. All participants completed visit 1 and visit 2, and adhered to pre-testing instructions.

Table 1: Participant Characteristics

Variable	Baseline Value
Men (#)	10
Women (#)	10
Age (years)	24.70 ± 5.13
Mass (kg)	74.16 ± 18.15
Height(cm)	171.67 ± 12.43
Resting SBP (mmHg)	107.93 ± 16.14
Resting DBP (mmHg)	58.68 ± 6.77
Resting HR (bpm)	66.01 ± 8.61

Note: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate. Values are mean ± standard deviation ($\bar{x}$ ± SD).

2.5.1 Comparison of Blood Pressure and Heart Rate

RMANCOVA revealed statistically significant BP and HR differences between devices, whereby SBP and DBP were higher when the IHG protocol was performed using the inflatable stress ball, yet there was a greater HR response to the Zona-performed protocol (all $p \leq 0.05$). Importantly, these differences disappeared after review of pairwise comparison analyses (see Table 2 and Appendix J, K, L). The details of the analyses are as follows:

With respect to SBP, interaction effects for device and time (F (3,48) = 4.52, $p = 0.007$); device and order (F (1,16) = 5.06, $p = 0.04$); device, time and

order (*F* (3,48) = 2.84, p = 0.05); and device, time and fitness (*F* (3,48) = 3.14, p = 0.03) were observed. As noted above, pairwise comparisons eliminated statistically significant differences in SBP between devices (F (1,16) = 5.980, p = 0.615). Main effects were also observed for time (*F* (3,48) = 3.31, p=0.03), device (*F* (1,16) = 5.98, p = 0.03), and sex (*F* (1,16) = 4.51, p = 0.05), yet pairwise analyses revealed sex to be the only meaningful comparison in that men had a significantly higher SBP response throughout the IHG protocols when compared to women ($\bar{x}$ ± SD (mmHg): 10.92 ± 1.13 for men and 7.40 ± 1.01 for women). Between-subject differences for device, time, order, and fitness were not observed.

Statistically significant differences in DBP were observed for both device (*F* (1,16) = 5.111, p = 0.038), and time (*F* (3,48) = 3.285, p = 0.029). Like SBP, pairwise comparison of each device denoted that although the inflatable stress ball elicited a slightly higher DBP throughout the protocol, this was not statistically significant (*F* (1,16) = 5.111, p = 0.35). However, unlike SBP, a main effect of time was observed such that DBP was significantly higher in IHG contraction 4 than it was during contraction 2 (CI 95%, 0.995 to 7.055, p = 0.006).

Regarding HR, statistically significant interactions were observed between device and order of device (*F* (1,16) = 22.91, p = 0.00), as were main effects for device (*F* (1,16) = 19.40, p = 0.00) and time (*F* (3,48) = 5.95, p = 0.00). In contrast to BP, pairwise comparison of the devices revealed a higher HR response when the IHG protocol was performed using the computerized device,

yet like SBP and DBP, this difference was not statistically significant (F (1,16) = 19.40, p = 0.73). Further, the effect of order dissipated upon examination of between-subjects effects (F (1,16) = 0.23, p = 0.64). No other meaningful pairwise comparisons were revealed.

Overall, when the covariates of sex, device order, and fitness were removed from the analysis, there were no statistically significant data to report between devices.

Table 2: Cardiovascular Effects

Variable	Computerized Device	Inflatable Stress Ball
SBP (mmHg)	8.23 ± 9.47	9.10 ± 7.36
DBP (mmHg)	7.13 ± 7.77	8.86 ± 9.90
HR (bpm)	6.98 ± 7.50	6.53 ± 8.20

Note: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate. Values are mean ± standard deviation ($\bar{x}$ ± SD).

2.5.2 Comparison of Subjective Rating of Perceived Exertion

Analysis by RMANCOVA indicated an interaction of time and sex (F (3,48) = 2.83, p = 0.048) for RPE, and main effects for time (F (3,48) = 4.81, p = 0.005) and fitness (F (1,16) = 5.062, p = 0.04). However, no main effects were observed for sex, order and device regarding RPE. Although initially statistically significant based on between-subjects interactions (F (1,16) = 5.062, p = 0.039), analysis of pairwise comparisons revealed a lack of effect of fitness on RPE. Moreover, pairwise comparison of devices indicated that the computerized device was perceived to require greater effort by 0.337 (CI 95%, -0.27 to 0.94), but this result was also not statistically significant (F (1,16) = 0.51, p = 0.26). In contrast, pairwise comparison of contractions revealed some statistically significant differences, but these differences were not meaningful (see Table 3).

Table 3: Subjective Rating of Perceived Exertion

Scale	Device	Grand Mean	Cont. 1	Cont. 2	Cont. 3	Cont. 4
RPE (1-10)	**Computerized**	+/- 5.76 1.83	+/- 5.25 1.80†‡	+/- 5.60 1.79†‡	+/- 6.05 1.93^{*+}	+/- 6.15 1.79^{*+}
RPE (1-10)	**Inflatable Stress Ball**	+/- 5.42 1.78	+/- 5.10 1.59†‡	+/- 5.00 1.69†‡	+/- 5.70 1.78^{*+}	+/- 5.90 2.02^{*+}

Note: Rating of perceived exertion (RPE). Values are mean ± standard deviation ($\bar{x}$ ± SD).
*Significant differences from contraction 1, $^{+}$Significant differences from contraction 2, †Significant differences from contraction 3, ‡Significant differences from contraction 4.

2.6 Discussion

The long-term effects of IHG training on BP have been well documented (Inder et al., 2016). However, widespread uptake and continued participation in this form of exercise training has been hindered by the barrier of accessibility, including cost, for the computerized device traditionally used. This study illustrated that a cost-effective alternative can replicate acute HR and BP results of more expensive and traditional IHG devices, laying a foundation for future training studies.

Seminal work by Millar et al., (2008) comparing a less expensive, alternative IHG device with the traditional, more expensive computerized model found that following an 8 week training protocol there were statistically significant decreases in both systolic and diastolic blood pressure (SBP and DBP). Although the alternate IHG device was effective, there were numerous drawbacks, and the notion of conducting research with other stand-alone, cost-effective devices emerged (Millar et al., 2008; Inder et al., 2016; Whelton et al., 2018). The current study adds to the literature as one of few studies examining the acute effects of

an IHG bout on the cardiovascular system, and concomitant RPE. Furthermore, it is the only known study to date to directly compare the traditional, costly computerized device with a cost-effective option such as an inflatable stress ball.

Data from the current study was comparable to previous studies when examining acute increases in BP during IHG exercise (Araujo et al., 2011; Olher et al., 2013). As hypothesized, there were no statistical differences observed between each device based on the examination of SBP, DBP, and HR. With no significant differences between devices this introduces that IHG using inflatable stress balls may facilitate a cost effective, widely available treatment opportunity for lowering BP worldwide (WHO, 2013; WHO, 2017). Future studies need to explore the long-term effect on BP adaptations with training.

Ratings of perceived exertion provide important insight into the potential for IHG. The current study offers support for long-term feasibility in that both devices elicit a similar engagement of perceived effort felt. Building on this exciting potential was the observation that 30% MVC equated to an RPE of 5-6 for each contraction, a finding similar to work of Morrin et al., (2018). A prominent limiting factor of the device investigated in the seminal work of Millar et al., (2008) was that trained personnel were required to regulate the IHG training intensity. Importantly, the current study provides insight into the ability of the participant to self-regulate IHG exercise without the computerized device. The possibility that an individual can use the inflatable stress ball, self-regulating 30% based on the scale (approximately a 6), and without trained personnel, raises the feasibility and effectiveness of the device.

Overall, this work provides evidence that individual effort given to engage in IHG exercise is the same for an inflatable stress ball as it was for the computerized device. Moreover, these findings in combination with implementation of the inflatable stress ball may allow a broader range of people to participate in IHG exercise due to the affordability and comfortability of the device, thereby addressing the call made by WHO (2017). Ultimately, this lays the foundation to have a global impact on reducing BP through scaling up of IHG training as a standard of care for the treatment of HTN with long-term adherence to this form of exercise more likely.

2.7 Research Impact and Future Directions

The current study demonstrated similar cardiovascular (HR and BP responses) and psychophysical (RPE) responses to a bout of IHG using a traditional computerized device and an alternative inexpensive inflatable stress ball. Thus, there are potential indications for promoting treatment compliance over the long-term using the inflatable stress ball, while adding to the weight of evidence recently provided by Morrin et al. (2018). These findings provide a foundation for future studies to test efficacy and outcome benefit, further promoting IHG as a treatment option for BP management.

Importantly, the current study is in alignment with the key health priorities of the WHO, which emphasizes enhanced feasibility, low maintenance, and inexpensive ways to effectively prevent, treat and manage HTN (WHO, 2017). In addition to providing an alternative device for the treatment of HTN worldwide, the current study and the potential implementation of the affordable inflatable

stress ball provides support to meet these needs. These findings are of a particular relevance to individuals residing in low to middle income countries (LMIC) where HTN rates contribute to 75% of the global disease burden (WHO, 2017). This high prevalence rate is concomitant to poorer rates of HTN awareness, treatment and control (Mills et al., 2015). Healthcare system-, provider- and/or patient-level barriers, such as lack of access to care, high provider burden, poor healthcare staffing, low patient health literacy, and lack of treatment adherence, are also contributing factors (Mills et al., 2015; Musinguzi et al., 2015). Taken together, implementation of cost effective, readily available BP-lowering treatments that work, have a low provider burden, and offer a high potential for uptake and long-term continuation are urgently needed in LMICs. The potential to offer IHG training using an inflatable stress ball as a BP-lowering standard of care treatment in primary care is timely and enticing.

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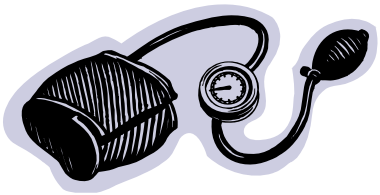
Appendices

Appendix A: Recruitment Poster, Email Script, Presentation Script

Do you think you have normal blood pressure?



If so, you may be eligible to participate in a study examining the effects of handgrip exercise on blood pressure.

If you are interested and would like more information please call: (519) -253-3000

ext. 4979 or email: richardu@uwindsor.ca

Jared Richards: richardu@uwindsor.ca 519-253-3000 ext. 4979	Jared Richards: richardu@uwindsor.ca 519-253-3000 ext. 4979	Jared Richards: richardu@uwindsor.ca 519-253-3000 ext. 4979	Jared Richards: richardu@uwindsor.ca 519-253-3000 ext. 4979	Jared Richards: richardu@uwindsor.ca 519-253-3000 ext. 4979	Jared Richards: richardu@uwindsor.ca 519-253-3000 ext. 4979	Jared Richards: richardu@uwindsor.ca 519-253-3000 ext. 4979	Jared Richard richardu uwinds ca 519-25 3000 ex 4979

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

Email to be sent by Sharon Horne, the Human Kinetics Administrative Assistant to Department Head and Graduate Program Secretary and Undergraduate Program Secretary after receiving the email from Mr. Richards along with a request to forward it to all Human Kinetics Students:

"Attention all people over the age of 18 years. If you think you have normal blood pressure, you may be eligible to participate in a research study being conducted by researchers in the Department of Kinesiology at the University of Windsor. We are investigating the effects of isometric (constant squeeze) handgrip exercise on your blood pressure and heart rate. For more information please contact Jared at 519-253-3000 ex. 4979 or richardu@uwindsor.ca"

Presentation to be delivered by Mr. Richards when speaking to a group of individuals from research laboratories, undergraduate classes and/or community exercise facilities

"Hello everyone, my name is Jared Richards, and I am a Master's Student at the University of Windsor conducting research in the Department of Kinesiology. My colleagues and I are investigating the effects of isometric, or constant squeeze, handgrip exercise on blood pressure and heart rate. We are looking to compare expensive computerized devices and cheaper alternatives, like stress balls, to see if they are different. If you are over the age of 18 and think you have normal blood pressure than you may be eligible to participate. Feel free to contact me by phone at 519-253-3000 ex. 4979 or by emailing me at richardu@uwindsor.ca. Thank you for your time.

Appendix B: Letter of Consent and Letter of Information

Note: Each of these are found on the pages following.

CONSENT TO PARTICIPATE IN RESEARCH

Title of Study: Getting the Best GRIP on Blood Pressure Control: Are Stress Balls and Handgrips Equally Effective?

You are invited to participate in a research study conducted by Mr. Jared Richards from the Faculty of Human Kinetics at the University of Windsor.

If you have any questions or concerns about the research, please feel to contact co-investigators Mr. Jared Richards BHK, MHK Candidate (richardu@uwindsor.ca), Dr. Cheri McGowan, PhD (mcgowanc@uwindsor.ca) and Dr. Paula van Wyk, PhD (pvanwyk@uwindsor.ca)

PURPOSE OF THE STUDY

Our research group and others have shown that isometric (constant squeeze) exercise training using a computerized isometric handgrip device (isometric handgrip, IHG) lowers resting blood pressure (BP) in younger and older people, and in those with and without high BP. Currently, computerized IHG is very expensive, therefore, it is important to determine if a store purchased inexpensive inflatable ball (similar to a stress ball) does something similar. The purpose of this study is to investigate if the two devices of differing costs cause similar body cardiovascular responses (e.g. BP and heart rate).

In order to participate in this study, you must have a normal BP (<135/85 mmHg), and you must be over 18 years old. If you have a disorder, or any known ailments, are a chronic smoker (nicotine, vaping, and/or marijuana), or are taking any medications that influence your cardiovascular system (other than the birth control pill) you may be ineligible to participate. If you have a physical limitation impairing your ability to exercise you may also be ineligible to participate.

PROCEDURES

If you volunteer to participate in this study, you will be invited to attend two lab sessions:

First Visit: Familiarization and Information Session (1 Hour)

You will meet with the study investigators at the Physical Activity and Cardiovascular Research (PACR) Laboratory (Room #240, Human Kinetics Building, University of Windsor, Windsor, Ontario, Canada) where you will receive a consent form and information sheet about the study. At this time, one of the study investigators will explain

all parts of the study. If you are still interested in participating in the study, you will sign the consent form and fill out two brief medical questionnaires. If you are still eligible to participate, you will then have your BP measured in your upper right arm, similar to how it is taken at a doctor's office. In brief, your resting BP will be measured in your upper right arm after 10 minutes of seated rest. Your BP will be measured 4 times, with 2 minutes of rest between measures. If you are still eligible to participate, you will then have an opportunity to practice all parts of the study.

Second Visit: Testing Day (1.5 Hours)

If you are still interested in participating in the study, you will visit the lab at least 24 hours following first visit.

In order to participate on the testing day ongoing consent will be needed. It is also important that you refrain from participation in strenuous exercise (e.g., difficult, high intensity exercise that causes heavy breathing, sweating, and muscle fatigue) for 24 hours before the testing day, and to avoid caffeine, consumption of alcohol, and over the counter medication for at least 12 hours before. All testing will be scheduled to take place 2 hours after your last meal, in a quiet, temperature-controlled room in the presence of the study investigators. You will be asked to go to the washroom prior to testing, as a full bladder can increase BP.

For the duration of the test, you will be asked to remain seated with your arms at a 90-degree angle placed on a table in front of you. You will be outfitted with a blood pressure cuff around your right arm to take BP and heart rate (HR) measurements. These measures will be collected continuously for 10 minutes prior to, during, and for at least 30 minutes following each isometric handgrip (IHG) bout. Next, you will be given 10 minutes of seated rest. Following the rest period, BP measurements will be taken in order to establish your baseline measurements. Following these measurements, your maximum voluntary contraction (MVC; hardest squeeze) will be calculated using each handgrip (traditional, computerized IHG and the inflatable ball) in order to determine the intensity to which the IHG bouts will be performed.

Next, you will be asked perform, in random order, an IHG protocol on the computerized IHG device and the store-bought inflatable ball. The protocols will be separated by a 30-minute rest period (minimum) or until your BP has returned to near resting values. In both conditions, the IHG bout will consist of 4, 2-minute bilateral (right and left) contractions at 30% of the MVC, each separated by 4-minute rest period. Following each 2-minute contraction, you will be asked to rate your level of perceived exertion using a 1-10 scale. Upon completion of the final bout of handgrip, there will a final stabilization period to ensure that your BP returns to near pre-exercise values.

POTENTIAL RISKS AND DISCOMFORTS

During the study, it is possible you may experience tingling in the upper arm due to the inflation of the blood pressure cuff, but this should subside when the cuff deflates. Muscle

fatigue in the hand may occur in the hand during the protocols due to the IHG bouts. However, because this is an acute single session study, proper technique and instruction will be given to participants, which results in minimal risk.

Please contact one of the study investigators if you feel any adverse effects from completing any portion of the study, and/or if you have any questions or concerns. If you experience any adverse effects during any testing procedure, first line response will be provided.

POTENTIAL BENEFITS TO PARTICIPANTS AND/OR TO SOCIETY

You may not experience any direct benefit by participating in this single session study, however you will learn how your heart rate and blood pressure changes during a bout of handgrip exercise. However, if we prove our theories, evidence of the equivalence of an inflatable ball in comparison to the traditional, more expensive computerized IHG may lay the groundwork for future studies investigating the use of affordable, commercially available handgrips as a means to lower BP.

COMPENSATION FOR PARTICIPATION

All participants will receive a Kinesiology Research item (e.g., T-shirt) of their choice upon completion of the study.

CONFIDENTIALITY

Any information that is obtained in connection with this study that can identify you will remain confidential.

To ensure your confidentiality, following your consent, you will be assigned a study code. Your name will not be mentioned in any publication or presentation, and you will be identified with only your study code on all collection tools (electronic or otherwise). All paper data will be stored in the locked laboratory (PACR Lab, Room #240, Human Kinetics Building, University of Windsor). Information stored on computer will be password-accessible only. With respect to final disposal, all paper records (including medical and physical activity readiness questionnaires) will be shredded after 5 years.

PARTICIPATION AND WITHDRAWAL

You can choose whether to be in this study or not, and your participation or lack of it will not influence your participation in another study. If you volunteer to be in this study, you may withdraw at any time prior to July 25th without consequences of any kind. The

investigator may withdraw you from this research if circumstances arise which warrant doing so. In any of the cases described above, you will still receive a Kinesiology research item of your choice.

FEEDBACK OF THE RESULTS OF THIS STUDY TO THE PARTICIPANTS

Results will be posted at the completion of the study on approximately August 25th under the University of Windsor's Research Ethics Board (REB) website at: http://www.uwindsor.ca/reb

SUBSEQUENT USE OF DATA

These data may be used in subsequent studies, in publications and in presentations. However, your privacy will be upheld with the use of your unique subject study code under all circumstances. Data may be used as a foundation for future study of store-bought, readily available IHG, and/or merged with other data sets for comparison.

RIGHTS OF RESEARCH PARTICIPANTS

If you have questions regarding your rights as a research participant, contact: Research Ethics Coordinator, University of Windsor, Windsor, Ontario, N9B 3P4; Telephone: 519-253-3000, ext. 3948; e-mail: ethics@uwindsor.ca

SIGNATURE OF RESEARCH PARTICIPANT/LEGAL REPRESENTATIVE

I understand the information provided for the study: *Getting the Best GRIP on Blood Pressure Control: Are Stress Balls and Handgrips Equally Effective*? *Response* as described herein. My questions have been answered to my satisfaction, and I agree to participate in this study. I have been given a copy of this form.

_____
Name of Participant

_____ _____
Signature of Participant Date

SIGNATURE OF INVESTIGATOR

These are the terms under which I will conduct research.

_____ _____

Signature of Investigator Date

Second Visit (Ongoing Consent):

I understand the information provided for the study: *Getting the Best GRIP on Blood Pressure Control: Are Stress Balls and Handgrips Equally Effective?* described herein. My questions have been answered to my satisfaction, and I agree to participate in this study. I consent (agree) to continue being a participant in this study.

_____

Name of Participant

_____ _____

Signature of Participant Date

_____ _____

Signature of Investigator Date

LETTER OF INFORMATION FOR CONSENT TO PARTICIPATE IN RESEARCH

Title of Study: Getting the Best GRIP on Blood Pressure Control: Are Stress Balls and Handgrips Equally Effective?

You are invited to participate in a research study conducted by Mr. Jared Richards from the Faculty of Human Kinetics at the University of Windsor.

If you have any questions or concerns about the research, please feel to contact co-investigators Mr. Jared Richards (richardu@uwindsor.ca), Dr. Cheri McGowan, PhD (mcgowanc@uwindsor.ca) and Dr. Paula van Wyk, PhD (pvanwyk@uwindsor.ca)

PURPOSE OF THE STUDY

Our research group has shown that isometric (constant squeeze) exercise training using a computerized isometric handgrip device (isometric handgrip, IHG) lowers resting blood pressure (BP) in younger and older people, and in those with and without high BP. Currently, computerized IHG is very expensive, therefore, it is important to determine if a store purchased inexpensive inflatable ball (similar to a stress ball) has similar results to the more expensive devices. The purpose of this study is to investigate if the two devices of differing costs cause similar body cardiovascular responses (e.g. BP rates).

In order to participate in this study, you must have a normal BP (<135/85 mmHg), and you must be over 18 years old. If you have a disorder or any known ailments, are a chronic smoker (nicotine, vaping, and/or marijuana), or are taking any medications that influence your cardiovascular system (other than the birth control pill) you may be ineligible to participate. If you have a physical limitation impairing your ability to exercise you may also be ineligible to participate.

PROCEDURES

If you volunteer to participate in this study, you will be invited to:

First Visit: Familiarization and Information Session (1 Hour)

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

Second Visit: Testing Day (1.5 Hours)

If you are still interested in participating in the study, you will visit the lab at least 24 hours following first visit.

In order to participate on the testing day ongoing consent will be needed. It is also it important that you refrain from participation in strenuous exercise (e.g., difficult, high intensity exercise that causes heavy breathing, sweating, and muscle fatigue) for 24 hours before the testing day, and to avoid caffeine, consumption of alcohol, and over the counter medication for at least 12 hours before. All testing will be scheduled to take place 2 hours after your last meal, in a quiet, temperature-controlled room in the presence of the study investigators. You will be asked to go to the washroom prior to testing, as a full bladder can increase BP.

For the duration of the test, you will be asked to remain seated with your arms at a 90-degree angle placed on a table in front of you. You will be outfitted with a blood pressure cuff around your right arm to take BP and heart rate (HR) measurements. These measures will be collected continuously for 10 minutes prior to, during, and for at least 30 minutes following each isometric handgrip (IHG) bout. Next, you will be given 10 minutes of seated rest. Following the rest period, BP measurements will be taken in order to establish your baseline measurements. Following these measurements, your maximum voluntary contraction (MVC; hardest squeeze) will be calculated using each handgrip (traditional, computerized IHG and the inflatable ball) in order to determine the intensity to which the IHG bouts will be performed.

Next, you will be asked perform, in random order, an IHG protocol on the computerized IHG device and the store-bought inflatable ball. The protocols will be separated by a 30-minute rest period (minimum) or until your BP has returned to near resting values. In both conditions, the IHG bout will consist of 4, 2-minute bilateral (right and left) contractions at 30% of the MVC, each separated by 4-minute rest period. Following each 2-minute contraction, you will be asked to rate your level of perceived exertion using a 1-10 scale. Upon completion of the final bout of handgrip, there will a final stabilization period to ensure that your BP returns to near pre-exercise values.

POTENTIAL RISKS AND DISCOMFORTS

During the study, it is possible you may experience tingling in the upper arm due to the inflation of the blood pressure cuff, but this should subside when the cuff deflates. Muscle fatigue in the hand may occur in the hand during the protocols due to the IHG bouts. However, because this is an acute single session study, proper technique and instruction will be given to participants, which results in minimal risk.

Please contact one of the study investigators if you feel any adverse effects from completing any portion of the study, and/or if you have any questions or concerns. If you experience any adverse effects during any testing procedure, first line response will be provided.

POTENTIAL BENEFITS TO PARTICIPANTS AND/OR TO SOCIETY

You may not experience any physical direct benefit by participating in this single session study. However, if we prove our theories, evidence of the equivalence of an inflatable ball in comparison to the traditional, more expensive computerized IHG may lay the groundwork for future studies investigating the use of affordable, commercially available handgrips as a means to lower BP.

COMPENSATION FOR PARTICIPATION

All participants will receive a Kinesiology Research item of their choice (e.g. shirt) upon completion of the study.

CONFIDENTIALITY

Any information that is obtained in connection with this study that can identify you will remain confidential.

To ensure your confidentiality, following your consent, you will be assigned a study code. Your name will not be mentioned in any publication or presentation, and you will be identified with only your study code on all collection tools (electronic or otherwise). All paper data will be stored in the locked laboratory (PACR Lab, Room #240, Human Kinetics Building, University of Windsor). Information stored on computer will be password-accessible only. With respect to final disposal, all paper records (including medical and physical activity readiness questionnaires) will be shredded after 5 years.

PARTICIPATION AND WITHDRAWAL

You can choose whether to be in this study or not, and your participation or lack of it will not influence your participation in another study. If you volunteer to be in this study, you may withdraw at any time prior to July 25th without consequences of any kind. The investigator may withdraw you from this research if circumstances arise which warrant doing so. In any of the cases described above, you will still receive a Kinesiology Research item of your choice.

FEEDBACK OF THE RESULTS OF THIS STUDY TO THE PARTICIPANTS

Results will be posted at the completion of the study on approximately August 25th under the University of Windsor's Research Ethics Board (REB) website at: http://www.uwindsor.ca/reb

SUBSEQUENT USE OF DATA

These data may be used in subsequent studies, in publications and in presentations however your privacy will be upheld with the use of your unique subject study code under all circumstances. Data may be used as a foundation for future study of store-bought, readily available IHG, and/or merged with other data sets for comparison.

RIGHTS OF RESEARCH PARTICIPANTS

If you have questions regarding your rights as a research participant, contact: Research Ethics Coordinator, University of Windsor, Windsor, Ontario, N9B 3P4; Telephone: 519-253-3000, ext. 3948; e-mail: ethics@uwindsor.ca

SIGNATURE OF INVESTIGATOR

These are the terms under which I will conduct research.

_____ _____

Signature of Investigator Date

Appendix C: Computerized IHG Device

a) Top view

b) Side view to show the area for the hand grip

Computerized Isometric Handgrip tool, Zona (Zona Series 3, Zona Health, Boise, ID, USA)

Appendix D: Inflatable Stress Ball

Inflatable Stress Ball (Part Number 020500, AllBall, Sportime, Thailand. www.Amazon.com)

Appendix E: Physical Activity Readiness Questionnaire Plus (PAR-Q +)

CSEP approved Sept 12 2011 version

PAR-Q+

The Physical Activity Readiness Questionnaire for Everyone

Regular physical activity is fun and healthy, and more people should become more physically active every day of the week. Being more physically active is very safe for MOST people. This questionnaire will tell you whether it is necessary for you to seek further advice from your doctor OR a qualified exercise professional before becoming more physically active.

SECTION 1 - GENERAL HEALTH

	Please read the 7 questions below carefully and answer each one honestly: check YES or NO.	YES	NO
1.	Has your doctor ever said that you have a heart condition OR high blood pressure?	☐	☐
2.	Do you feel pain in your chest at rest, during your daily activities of living, OR when you do physical activity?	☐	☐
3.	Do you lose balance because of dizziness OR have you lost consciousness in the last 12 months? Please answer NO if your dizziness was associated with over-breathing (including during vigorous exercise).	☐	☐
4.	Have you ever been diagnosed with another chronic medical condition (other than heart disease or high blood pressure)?	☐	☐
5.	Are you currently taking prescribed medications for a chronic medical condition?	☐	☐
6.	Do you have a bone or joint problem that could be made worse by becoming more physically active? Please answer NO if you had a joint problem in the past, but it does not limit your current ability to be physically active. For example, knee, ankle, shoulder or other.	☐	☐
7.	Has your doctor ever said that you should only do medically supervised physical activity?	☐	☐

If you answered NO to all of the questions above, you are cleared for physical activity.

Go to Section 3 to sign the form. You do not need to complete Section 2.

- Start becoming much more physically active – start slowly and build up gradually.
- Follow the Canadian Physical Activity Guidelines for your age (www.csep.ca/guidelines).
- You may take part in a health and fitness appraisal.
- If you have any further questions, contact a qualified exercise professional such as a CSEP Certified Exercise Physiologist® (CSEP-CEP) or CSEP Certified Personal Trainer® (CSEP-CPT).
- If you are over the age of 45 yrs. and NOT accustomed to regular vigorous physical activity, please consult a qualified exercise professional (CSEP-CEP) before engaging in maximal effort exercise.

If you answered YES to one or more of the questions above, please GO TO SECTION 2.

Delay becoming more active if:

- You are not feeling well because of a temporary illness such as a cold or fever – wait until you feel better
- You are pregnant – talk to your health care practitioner, your physician, a qualified exercise professional, and/or complete the PARmed-X for Pregnancy before becoming more physically active OR
- Your health changes – please answer the questions on Section 2 of this document and/or talk to your doctor or qualified exercise professional (CSEP-CEP or CSEP-CPT) before continuing with any physical activity programme.

CSEP | SCPE

SECTION 2 - CHRONIC MEDICAL CONDITIONS

Please read the questions below carefully and answer each one honestly: check YES or NO.			YES	NO
1.	Do you have Arthritis, Osteoporosis, or Back Problems?		☐ If yes, answer questions 1a-1c	☐ If no, go to question 2
	1a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	☐	☐
	1b.	Do you have joint problems causing pain, a recent fracture or fracture caused by osteoporosis or cancer, displaced vertebra (e.g., spondylolisthesis), and/or spondylolysis/pars defect (a crack in the bony ring on the back of the spinal column)?	☐	☐
	1c.	Have you had steroid injections or taken steroid tablets regularly for more than 3 months?	☐	☐
2.	Do you have Cancer of any kind?		☐ If yes, answer questions 2a-2b	☐ If no, go to question 3
	2a.	Does your cancer diagnosis include any of the following types: lung/bronchogenic, multiple myeloma (cancer of plasma cells), head, and neck?	☐	☐
	2b.	Are you currently receiving cancer therapy (such as chemotherapy or radiotherapy)?	☐	☐
3.	Do you have Heart Disease or Cardiovascular Disease? This includes Coronary Artery Disease, High Blood Pressure, Heart Failure, Diagnosed Abnormality of Heart Rhythm		☐ If yes, answer questions 3a-3e	☐ If no, go to question 4
	3a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	☐	☐
	3b.	Do you have an irregular heart beat that requires medical management? (e.g. atrial fibrillation, premature ventricular contraction)	☐	☐
	3c.	Do you have chronic heart failure?	☐	☐
	3d.	Do you have a resting blood pressure equal to or greater than 160/90 mmHg with or without medication? (Answer YES if you do not know your resting blood pressure)	☐	☐
	3e.	Do you have diagnosed coronary artery (cardiovascular) disease and have not participated in regular physical activity in the last 2 months?	☐	☐
4.	Do you have any Metabolic Conditions? This includes Type 1 Diabetes, Type 2 Diabetes, Pre-Diabetes		☐ If yes, answer questions 4a-4c	☐ If no, go to question 5
	4a.	Is your blood sugar often above 13.0 mmol/L? (Answer YES if you are not sure)	☐	☐
	4b.	Do you have any signs or symptoms of diabetes complications such as heart or vascular disease and/or complications affecting your eyes, kidneys, and the sensation in your toes and feet?	☐	☐
	4c.	Do you have other metabolic conditions (such as thyroid disorders, pregnancy-related diabetes, chronic kidney disease, liver problems)?	☐	☐
5.	Do you have any Mental Health Problems or Learning Difficulties? This includes Alzheimer's, Dementia, Depression, Anxiety Disorder, Eating Disorder, Psychotic Disorder, Intellectual Disability, Down Syndrome)		☐ If yes, answer questions 5a-5b	☐ If no, go to question 6
	5a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	☐	☐
	5b.	Do you also have back problems affecting nerves or muscles?	☐	☐

Please read the questions below carefully and answer each one honestly: check YES or NO.			YES	NO
6.	Do you have a Respiratory Disease? This includes Chronic Obstructive Pulmonary Disease, Asthma, Pulmonary High Blood Pressure		☐ If yes, answer questions 6a-6d	☐ If no, go to question 7
	6a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	☐	☐
	6b.	Has your doctor ever said your blood oxygen level is low at rest or during exercise and/or that you require supplemental oxygen therapy?	☐	☐
	6c.	If asthmatic, do you currently have symptoms of chest tightness, wheezing, laboured breathing, consistent cough (more than 2 days/week), or have you used your rescue medication more than twice in the last week?	☐	☐
	6d.	Has your doctor ever said you have high blood pressure in the blood vessels of your lungs?	☐	☐
7.	Do you have a Spinal Cord Injury? This includes Tetraplegia and Paraplegia		☐ If yes, answer questions 7a-7c	☐ If no, go to question 8
	7a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	☐	☐
	7b.	Do you commonly exhibit low resting blood pressure significant enough to cause dizziness, light-headedness, and/or fainting?	☐	☐
	7c.	Has your physician indicated that you exhibit sudden bouts of high blood pressure (known as Autonomic Dysreflexia)?	☐	☐
8.	Have you had a Stroke? This includes Transient Ischemic Attack (TIA) or Cerebrovascular Event		☐ If yes, answer questions 8a-c	☐ If no, go to question 9
	8a.	Do you have difficulty controlling your condition with medications or other physician-prescribed therapies? (Answer NO if you are not currently taking medications or other treatments)	☐	☐
	8b.	Do you have any impairment in walking or mobility?	☐	☐
	8c.	Have you experienced a stroke or impairment in nerves or muscles in the past 6 months?	☐	☐
9.	Do you have any other medical condition not listed above or do you live with two chronic conditions?		☐ If yes, answer questions 9a-c	☐ If no, read the advice on page 4
	9a.	Have you experienced a blackout, fainted, or lost consciousness as a result of a head injury within the last 12 months OR have you had a diagnosed concussion within the last 12 months?	☐	☐
	9b.	Do you have a medical condition that is not listed (such as epilepsy, neurological conditions, kidney problems)?	☐	☐
	9c.	Do you currently live with two chronic conditions?	☐	☐

Please proceed to Page 4 for recommendations for your current medical condition and sign this document.

PAR-Q+

If you answered NO to all of the follow-up questions about your medical condition, you are ready to become more physically active:

- It is advised that you consult a qualified exercise professional (e.g., a CSEP-CEP or CSEP-CPT) to help you develop a safe and effective physical activity plan to meet your health needs.
- You are encouraged to start slowly and build up gradually – 20-60 min. of low- to moderate-intensity exercise, 3-5 days per week including aerobic and muscle strengthening exercises.
- As you progress, you should aim to accumulate 150 minutes or more of moderate-intensity physical activity per week.
- If you are over the age of 45 yrs. and NOT accustomed to regular vigorous physical activity, please consult a qualified exercise professional (CSEP-CEP) before engaging in maximal effort exercise.

If you answered YES to one or more of the follow-up questions about your medical condition:

- You should seek further information from a licensed health care professional before becoming more physically active or engaging in a fitness appraisal and/or visit a or qualified exercise professional (CSEP-CEP) for further information.

Delay becoming more active if:

- You are not feeling well because of a temporary illness such as a cold or fever – wait until you feel better
- You are pregnant - talk to your health care practitioner, your physician, a qualified exercise profesional, and/or complete the PARmed-X for Pregnancy before becoming more physically active OR
- Your health changes - please talk to your doctor or qualified exercise professional (CSEP-CEP) before continuing with any physical activity programme.

SECTION 3 - DECLARATION

- You are encouraged to photocopy the PAR-Q+. You must use the entire questionnaire and NO changes are permitted.
- The Canadian Society for Exercise Physiology, the PAR-Q+ Collaboration, and their agents assume no liability for persons who undertake physical activity. If in doubt after completing the questionnaire, consult your doctor prior to physical activity.
- If you are less than the legal age required for consent or require the assent of a care provider, your parent, guardian or care provider must also sign this form.
- Please read and sign the declaration below:

I, the undersigned, have read, understood to my full satisfaction and completed this questionnaire. I acknowledge that this physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if my condition changes. I also acknowledge that a Trustee (such as my employer, community/fitness centre, health care provider, or other designate) may retain a copy of this form for their records. In these instances, the Trustee will be required to adhere to local, national, and informational guidelines regarding the storage of personal health information ensuring that they maintain the privacy of the information and do not misuse or wrongfully disclose such information.

NAME _____ DATE _____

SIGNATURE _____ WITNESS _____

SIGNATURE OF PARENT/GUARDIAN/CARE PROVIDER _____

For more information, please contact:
Canadian Society for Exercise Physiology
www.csep.ca

KEY REFERENCES
1. Jamnik VJ, Warburton DER, Makarski J, McKenzie DC, Shephard RJ, Stone J, and Gledhill N. Enhancing the cectiveness of clearance for physical activity participation: background and overall process. APNM 36(S1):S3-S13, 2011.
2. Warburton DER, Gledhill N, Jamnik VK, Bredin SSD, McKenzie DC, Stone J, Charlesworth S, and Shephard RJ. Evidence-based risk assessment and recommendations for physical activity clearance; Consensus Document. APNM 36(S1):S266-s298, 2011.

The PAR-Q+ was created using the evidence-based AGREE process (1) by the PAR-Q+Collaboration chaired by Dr. Darren E. R. Warburton with Dr. Norman Gledhill, Dr. Veronica Jamnik, and Dr. Donald C. McKenzie (2). Production of this document has been made possible through financial contributions from the Public Health Agency of Canada and the BC Ministry of Health Services. The views expressed herein do not necessarily represent the views of the Public Health Agency of Canada or BC Ministry of Health Services.

CSEP approved Sept 12 2011 version

Appendix F: Intake Medical Questionnaire

Participant Code: _____ Date of Birth (MM/YYYY): _____ Height: _____
Mass: _____ Phone: (___) _____ Postal Code: _____

FOR EMERGENCY Notify: Relationship:
Address:_____
Phone: (___) _____

Family Doctor's Name: _____ Date of Last Physical: _____

Please Check YES or NO for each of the following:	YES	NO
1. Have you ever been hospitalized?..... - If YES, please specify:		
Have you ever had surgery?..... - If YES, please specify:		
2. Are you presently taking any medications or pills (including aspirin and other over-the-counter medications?..... - If YES, please specify:		
Are you presently taking any vitamins, supplements, and/or herbal supplements?.....		
3. Do you have any allergies (medicine, food, bees or other stinging insects)?..... - If YES, please specify:		
4. Have you ever passed out during or after exercise?.....		
Have you ever been dizzy during or after exercise?.....		
Have you ever had chest pain during or after exercise?.....		
Do you have high blood pressure (hypertension) or low blood pressure (hypotension)?.....		
Have you ever been told that you have a kidney problem?.....		
Have you ever been told that you have joint instability?.....		
Have you ever been told that you have a stomach problem?.....		
Have you ever been told that you have a heart problem?.....		
Have you ever been told that you have a heart murmur?.....		
Do you have a machine that regulated your heart beat?.....		
Have you ever had racing of your heart or skipped heartbeats?.....		
Has anyone in your family died of heart problems or a sudden death before age 50 years?.....		
5. Do you have any skin problems (itching, rashes, acne)?.....		
If you get a cut, does it take you a long time to stop bleeding?.....		
If you experience a blow to a muscle, do you bruise easily?.....		
6. Do you have Diabetes?.....		
7. Do you have Asthma or any other breathing problems?..... - If YES, please specify:		
8. Do you have any type of cardiovascular disease?..... - If YES, please specify:		
9. Have you had any other medical problems (infectious mononucleosis, etc.)?.....		
10. Have you had any medical problems since your last physical?.....		
11. Do you smoke?.....		
12. Do you aerobically exercise (e.g. walking) for $\geq$ 30 minutes, > 2 times per week?.....		
13. Do you currently take any birth control medications?..... - If YES, please specify:		
14. Date of last menstrual cycle:		
Please explain any physical limitations that may prevent you from completing this study?		

Appendix G: Automated Oscillometry Device / DINAMAP

(Dinamap Carescape v100, Critikon 23-33 cm cuff, Tampa, Florida, USA)

Appendix H: Digital Air Pressure Gauge

Used to determine MVC with the inflatable ball
Digital Ball Gauge (Fox 40 International, 340 Grays Road, Hamilton, Ontario, Canada, 2016)

Appendix I: Borg CR-10 Scale (RPE)

Appendix J: Systolic Blood Pressure Results

Mauchly's Test of Sphericity[a]

Measure: MEASURE_1

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[b] Greenhouse-Geisser
Device	1.000	.000	0	.	1.000
Time	.494	10.371	5	.066	.752
Device * Time	.586	7.859	5	.165	.747

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Device	Sphericity Assumed	697.925	1	697.925	5.980	.026	.272	5.980	.632
	Greenhouse-Geisser	697.925	1.000	697.925	5.980	.026	.272	5.980	.632
	Huynh-Feldt	697.925	1.000	697.925	5.980	.026	.272	5.980	.632
	Lower-bound	697.925	1.000	697.925	5.980	.026	.272	5.980	.632
Device * SEX	Sphericity Assumed	10.361	1	10.361	.089	.770	.006	.089	.059
	Greenhouse-Geisser	10.361	1.000	10.361	.089	.770	.006	.089	.059
	Huynh-Feldt	10.361	1.000	10.361	.089	.770	.006	.089	.059
	Lower-bound	10.361	1.000	10.361	.089	.770	.006	.089	.059
Device * Option	Sphericity Assumed	590.340	1	590.340	5.058	.039	.240	5.058	.561
	Greenhouse-Geisser	590.340	1.000	590.340	5.058	.039	.240	5.058	.561
	Huynh-Feldt	590.340	1.000	590.340	5.058	.039	.240	5.058	.561
	Lower-bound	590.340	1.000	590.340	5.058	.039	.240	5.058	.561
Device * Fitness	Sphericity Assumed	295.696	1	295.696	2.534	.131	.137	2.534	.322
	Greenhouse-Geisser	295.696	1.000	295.696	2.534	.131	.137	2.534	.322
	Huynh-Feldt	295.696	1.000	295.696	2.534	.131	.137	2.534	.322
	Lower-bound	295.696	1.000	295.696	2.534	.131	.137	2.534	.322
Error(Device)	Sphericity Assumed	1867.354	16	116.710					
	Greenhouse-Geisser	1867.354	16.000	116.710					
	Huynh-Feldt	1867.354	16.000	116.710					
	Lower-bound	1867.354	16.000	116.710					
Time	Sphericity Assumed	452.150	3	150.717	3.310	.028	.171	9.930	.719
	Greenhouse-Geisser	452.150	2.255	200.542	3.310	.043	.171	7.463	.624
	Huynh-Feldt	452.150	3.000	150.717	3.310	.028	.171	9.930	.719
	Lower-bound	452.150	1.000	452.150	3.310	.088	.171	3.310	.402

Time * SEX	Sphericity Assumed	264.266	3	88.089	1.935	.137	.108	5.804	.468
	Greenhouse-Geisser	264.266	2.255	117.210	1.935	.155	.108	4.362	.397
	Huynh-Feldt	264.266	3.000	88.089	1.935	.137	.108	5.804	.468
	Lower-bound	264.266	1.000	264.266	1.935	.183	.108	1.935	.258
Time * Option	Sphericity Assumed	83.673	3	27.891	.613	.610	.037	1.838	.168
	Greenhouse-Geisser	83.673	2.255	37.112	.613	.566	.037	1.381	.150
	Huynh-Feldt	83.673	3.000	27.891	.613	.610	.037	1.838	.168
	Lower-bound	83.673	1.000	83.673	.613	.445	.037	.613	.114
Time * Fitness	Sphericity Assumed	139.985	3	46.662	1.025	.390	.060	3.074	.261
	Greenhouse-Geisser	139.985	2.255	62.088	1.025	.377	.060	2.310	.226
	Huynh-Feldt	139.985	3.000	46.662	1.025	.390	.060	3.074	.261
	Lower-bound	139.985	1.000	139.985	1.025	.326	.060	1.025	.159
Error(Time)	Sphericity Assumed	2185.615	48	45.534					
	Greenhouse-Geisser	2185.615	36.074	60.587					
	Huynh-Feldt	2185.615	48.000	45.534					
	Lower-bound	2185.615	16.000	136.601					
Device * Time	Sphericity Assumed	587.052	3	195.684	4.515	.007	.220	13.545	.856
	Greenhouse-Geisser	587.052	2.241	262.004	4.515	.015	.220	10.116	.767
	Huynh-Feldt	587.052	3.000	195.684	4.515	.007	.220	13.545	.856
	Lower-bound	587.052	1.000	587.052	4.515	.050	.220	4.515	.515
Device * Time * SEX	Sphericity Assumed	278.175	3	92.725	2.139	.108	.118	6.418	.512
	Greenhouse-Geisser	278.175	2.241	124.151	2.139	.127	.118	4.794	.433
	Huynh-Feldt	278.175	3.000	92.725	2.139	.108	.118	6.418	.512
	Lower-bound	278.175	1.000	278.175	2.139	.163	.118	2.139	.280
Device * Time * Option	Sphericity Assumed	369.855	3	123.285	2.844	.047	.151	8.533	.646
	Greenhouse-Geisser	369.855	2.241	165.068	2.844	.066	.151	6.373	.552
	Huynh-Feldt	369.855	3.000	123.285	2.844	.047	.151	8.533	.646
	Lower-bound	369.855	1.000	369.855	2.844	.111	.151	2.844	.354
Device * Time * Fitness	Sphericity Assumed	408.790	3	136.263	3.144	.034	.164	9.432	.695
	Greenhouse-Geisser	408.790	2.241	182.445	3.144	.050	.164	7.044	.598
	Huynh-Feldt	408.790	3.000	136.263	3.144	.034	.164	9.432	.695
	Lower-bound	408.790	1.000	408.790	3.144	.095	.164	3.144	.385
Error(Device*Time)	Sphericity Assumed	2080.410	48	43.342					
	Greenhouse-Geisser	2080.410	35.850	58.031					
	Huynh-Feldt	2080.410	48.000	43.342					
	Lower-bound	2080.410	16.000	130.026					

a. Computed using alpha = .05

Tests of Between-Subjects Effects

Measure: MEASURE_1
Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	856.767	1	856.767	11.174	.004	.411
SEX	345.676	1	345.676	4.508	.050	.220
Option	54.038	1	54.038	.705	.414	.042
Fitness	151.336	1	151.336	1.974	.179	.110
Error	1226.814	16	76.676			

Pairwise Comparisons

Measure: MEASURE_1

(I) Device	(J) Device	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
1	2	-.875	1.708	.615	-4.496	2.746
2	1	.875	1.708	.615	-2.746	4.496

Based on estimated marginal means
a. Adjustment for multiple comparisons: Bonferroni.

Pairwise Comparisons

Measure: MEASURE_1

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
1	2	-1.975	1.434	1.000	-6.288	2.338
	3	-1.550	.908	.642	-4.280	1.180
	4	-5.125	1.796	.069	-10.528	.278
2	1	1.975	1.434	1.000	-2.338	6.288
	3	.425	1.602	1.000	-4.395	5.245
	4	-3.150	1.514	.324	-7.705	1.405
3	1	1.550	.908	.642	-1.180	4.280
	2	-.425	1.602	1.000	-5.245	4.395
	4	-3.575	1.642	.268	-8.514	1.364
4	1	5.125	1.796	.069	-.278	10.528
	2	3.150	1.514	.324	-1.405	7.705
	3	3.575	1.642	.268	-1.364	8.514

Based on estimated marginal means
a. Adjustment for multiple comparisons: Bonferroni.

Appendix K: Diastolic Blood Pressure Results

Mauchly's Test of Sphericity[a]

Measure: MEASURE_1

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[b] Greenhouse-Geisser
Device	1.000	.000	0	.	1.000
Time	.652	6.305	5	.279	.776
Device * Time	.464	11.310	5	.046	.702

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Device	Sphericity Assumed	655.809	1	655.809	5.111	.038	.242	5.111	.565
	Greenhouse-Geisser	655.809	1.000	655.809	5.111	.038	.242	5.111	.565
	Huynh-Feldt	655.809	1.000	655.809	5.111	.038	.242	5.111	.565
	Lower-bound	655.809	1.000	655.809	5.111	.038	.242	5.111	.565
Device * SEX	Sphericity Assumed	329.576	1	329.576	2.569	.129	.138	2.569	.326
	Greenhouse-Geisser	329.576	1.000	329.576	2.569	.129	.138	2.569	.326
	Huynh-Feldt	329.576	1.000	329.576	2.569	.129	.138	2.569	.326
	Lower-bound	329.576	1.000	329.576	2.569	.129	.138	2.569	.326
Device * Option	Sphericity Assumed	330.025	1	330.025	2.572	.128	.138	2.572	.326
	Greenhouse-Geisser	330.025	1.000	330.025	2.572	.128	.138	2.572	.326
	Huynh-Feldt	330.025	1.000	330.025	2.572	.128	.138	2.572	.326
	Lower-bound	330.025	1.000	330.025	2.572	.128	.138	2.572	.326
Device * Fitness	Sphericity Assumed	20.553	1	20.553	.160	.694	.010	.160	.066
	Greenhouse-Geisser	20.553	1.000	20.553	.160	.694	.010	.160	.066
	Huynh-Feldt	20.553	1.000	20.553	.160	.694	.010	.160	.066
	Lower-bound	20.553	1.000	20.553	.160	.694	.010	.160	.066
Error(Device)	Sphericity Assumed	2052.853	16	128.303					
	Greenhouse-Geisser	2052.853	16.000	128.303					
	Huynh-Feldt	2052.853	16.000	128.303					
	Lower-bound	2052.853	16.000	128.303					
Time	Sphericity Assumed	257.801	3	85.934	3.285	.029	.170	9.856	.716
	Greenhouse-Geisser	257.801	2.327	110.796	3.285	.042	.170	7.645	.631
	Huynh-Feldt	257.801	3.000	85.934	3.285	.029	.170	9.856	.716
	Lower-bound	257.801	1.000	257.801	3.285	.089	.170	3.285	.399
Time * SEX	Sphericity Assumed	62.676	3	20.892	.799	.501	.048	2.396	.209
	Greenhouse-Geisser	62.676	2.327	26.936	.799	.474	.048	1.859	.186

	Huynh-Feldt	62.676	3.000	20.892	.799	.501	.048	2.396	.209
	Lower-bound	62.676	1.000	62.676	.799	.385	.048	.799	.134
Time * Option	Sphericity Assumed	76.969	3	25.656	.981	.410	.058	2.943	.251
	Greenhouse-Geisser	76.969	2.327	33.079	.981	.395	.058	2.282	.221
	Huynh-Feldt	76.969	3.000	25.656	.981	.410	.058	2.943	.251
	Lower-bound	76.969	1.000	76.969	.981	.337	.058	.981	.154
Time * Fitness	Sphericity Assumed	210.588	3	70.196	2.684	.057	.144	8.051	.618
	Greenhouse-Geisser	210.588	2.327	90.505	2.684	.074	.144	6.245	.538
	Huynh-Feldt	210.588	3.000	70.196	2.684	.057	.144	8.051	.618
	Lower-bound	210.588	1.000	210.588	2.684	.121	.144	2.684	.338
Error(Time)	Sphericity Assumed	1255.481	48	26.156					
	Greenhouse-Geisser	1255.481	37.229	33.723					
	Huynh-Feldt	1255.481	48.000	26.156					
	Lower-bound	1255.481	16.000	78.468					
Device * Time	Sphericity Assumed	126.433	3	42.144	1.475	.233	.084	4.425	.365
	Greenhouse-Geisser	126.433	2.106	60.037	1.475	.243	.084	3.106	.300
	Huynh-Feldt	126.433	2.887	43.788	1.475	.235	.084	4.259	.357
	Lower-bound	126.433	1.000	126.433	1.475	.242	.084	1.475	.208
Device * Time * SEX	Sphericity Assumed	12.295	3	4.098	.143	.933	.009	.430	.074
	Greenhouse-Geisser	12.295	2.106	5.839	.143	.877	.009	.302	.071
	Huynh-Feldt	12.295	2.887	4.258	.143	.928	.009	.414	.074
	Lower-bound	12.295	1.000	12.295	.143	.710	.009	.143	.065
Device * Time * Option	Sphericity Assumed	116.847	3	38.949	1.363	.265	.079	4.089	.340
	Greenhouse-Geisser	116.847	2.106	55.486	1.363	.270	.079	2.871	.279
	Huynh-Feldt	116.847	2.887	40.468	1.363	.266	.079	3.936	.332
	Lower-bound	116.847	1.000	116.847	1.363	.260	.079	1.363	.196
Device * Time * Fitness	Sphericity Assumed	49.701	3	16.567	.580	.631	.035	1.739	.161
	Greenhouse-Geisser	49.701	2.106	23.601	.580	.574	.035	1.221	.140
	Huynh-Feldt	49.701	2.887	17.213	.580	.625	.035	1.674	.159
	Lower-bound	49.701	1.000	49.701	.580	.457	.035	.580	.111
Error(Device*Time)	Sphericity Assumed	1371.518	48	28.573					
	Greenhouse-Geisser	1371.518	33.694	40.705					
	Huynh-Feldt	1371.518	46.199	29.687					
	Lower-bound	1371.518	16.000	85.720					

a. Computed using alpha = .05

Tests of Between-Subjects Effects

Measure: MEASURE_1
Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	901.207	1	901.207	2.460	.136	.133
SEX	130.007	1	130.007	.355	.560	.022
Option	2.239	1	2.239	.006	.939	.000
Fitness	79.651	1	79.651	.217	.647	.013
Error	5861.906	16	366.369			

Pairwise Comparisons

Measure: MEASURE_1

(I) Device	(J) Device	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
1	2	-1.738	1.791	.346	-5.534	2.059
2	1	1.738	1.791	.346	-2.059	5.534

Based on estimated marginal means
a. Adjustment for multiple comparisons: Bonferroni.

Pairwise Comparisons

Measure: MEASURE_1

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[b]	95% Confidence Interval for Difference[b]	
					Lower Bound	Upper Bound
1	2	1.200	1.011	1.000	-1.842	4.242
	3	-1.550	1.013	.874	-4.598	1.498
	4	-2.825	1.472	.438	-7.253	1.603
2	1	-1.200	1.011	1.000	-4.242	1.842
	3	-2.750	1.004	.088	-5.771	.271
	4	-4.025*	1.007	.006	-7.055	-.995
3	1	1.550	1.013	.874	-1.498	4.598
	2	2.750	1.004	.088	-.271	5.771
	4	-1.275	1.268	1.000	-5.089	2.539
4	1	2.825	1.472	.438	-1.603	7.253
	2	4.025*	1.007	.006	.995	7.055
	3	1.275	1.268	1.000	-2.539	5.089

Based on estimated marginal means
*. The mean difference is significant at the .05 level.
b. Adjustment for multiple comparisons: Bonferroni.

Appendix L: Heart Rate Results

Mauchly's Test of Sphericity[a]

Measure: MEASURE_1

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[b] Greenhouse-Geisser
Device	1.000	.000	0	.	1.000
Time	.655	6.230	5	.285	.833
Device * Time	.855	2.299	5	.807	.901

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Device	Sphericity Assumed	1299.683	1	1299.683	19.402	.000	.548	19.402	.985
	Greenhouse-Geisser	1299.683	1.000	1299.683	19.402	.000	.548	19.402	.985
	Huynh-Feldt	1299.683	1.000	1299.683	19.402	.000	.548	19.402	.985
	Lower-bound	1299.683	1.000	1299.683	19.402	.000	.548	19.402	.985
Device * SEX	Sphericity Assumed	124.112	1	124.112	1.853	.192	.104	1.853	.249
	Greenhouse-Geisser	124.112	1.000	124.112	1.853	.192	.104	1.853	.249
	Huynh-Feldt	124.112	1.000	124.112	1.853	.192	.104	1.853	.249
	Lower-bound	124.112	1.000	124.112	1.853	.192	.104	1.853	.249
Device * Option	Sphericity Assumed	1534.601	1	1534.601	22.909	.000	.589	22.909	.994
	Greenhouse-Geisser	1534.601	1.000	1534.601	22.909	.000	.589	22.909	.994
	Huynh-Feldt	1534.601	1.000	1534.601	22.909	.000	.589	22.909	.994
	Lower-bound	1534.601	1.000	1534.601	22.909	.000	.589	22.909	.994
Device * Fitness	Sphericity Assumed	186.122	1	186.122	2.779	.115	.148	2.779	.347
	Greenhouse-Geisser	186.122	1.000	186.122	2.779	.115	.148	2.779	.347
	Huynh-Feldt	186.122	1.000	186.122	2.779	.115	.148	2.779	.347
	Lower-bound	186.122	1.000	186.122	2.779	.115	.148	2.779	.347
Error(Device)	Sphericity Assumed	1071.778	16	66.986					
	Greenhouse-Geisser	1071.778	16.000	66.986					
	Huynh-Feldt	1071.778	16.000	66.986					
	Lower-bound	1071.778	16.000	66.986					
Time	Sphericity Assumed	517.773	3	172.591	5.947	.002	.271	17.842	.940
	Greenhouse-Geisser	517.773	2.500	207.113	5.947	.003	.271	14.868	.904
	Huynh-Feldt	517.773	3.000	172.591	5.947	.002	.271	17.842	.940
	Lower-bound	517.773	1.000	517.773	5.947	.027	.271	5.947	.630

Time * SEX	Sphericity Assumed	154.012	3	51.337	1.769	.166	.100	5.307	.432
	Greenhouse-Geisser	154.012	2.500	61.606	1.769	.176	.100	4.423	.389
	Huynh-Feldt	154.012	3.000	51.337	1.769	.166	.100	5.307	.432
	Lower-bound	154.012	1.000	154.012	1.769	.202	.100	1.769	.240
Time * Option	Sphericity Assumed	196.354	3	65.451	2.255	.094	.124	6.766	.536
	Greenhouse-Geisser	196.354	2.500	78.543	2.255	.107	.124	5.639	.483
	Huynh-Feldt	196.354	3.000	65.451	2.255	.094	.124	6.766	.536
	Lower-bound	196.354	1.000	196.354	2.255	.153	.124	2.255	.292
Time * Fitness	Sphericity Assumed	215.626	3	71.875	2.477	.073	.134	7.430	.579
	Greenhouse-Geisser	215.626	2.500	86.252	2.477	.085	.134	6.192	.523
	Huynh-Feldt	215.626	3.000	71.875	2.477	.073	.134	7.430	.579
	Lower-bound	215.626	1.000	215.626	2.477	.135	.134	2.477	.316
Error(Time)	Sphericity Assumed	1392.924	48	29.019					
	Greenhouse-Geisser	1392.924	39.999	34.824					
	Huynh-Feldt	1392.924	48.000	29.019					
	Lower-bound	1392.924	16.000	87.058					
Device * Time	Sphericity Assumed	119.648	3	39.883	1.571	.209	.089	4.714	.387
	Greenhouse-Geisser	119.648	2.702	44.281	1.571	.213	.089	4.246	.365
	Huynh-Feldt	119.648	3.000	39.883	1.571	.209	.089	4.714	.387
	Lower-bound	119.648	1.000	119.648	1.571	.228	.089	1.571	.218
Device * Time * SEX	Sphericity Assumed	38.366	3	12.789	.504	.681	.031	1.512	.145
	Greenhouse-Geisser	38.366	2.702	14.199	.504	.663	.031	1.361	.139
	Huynh-Feldt	38.366	3.000	12.789	.504	.681	.031	1.512	.145
	Lower-bound	38.366	1.000	38.366	.504	.488	.031	.504	.102
Device * Time * Option	Sphericity Assumed	90.539	3	30.180	1.189	.324	.069	3.567	.299
	Greenhouse-Geisser	90.539	2.702	33.508	1.189	.323	.069	3.213	.282
	Huynh-Feldt	90.539	3.000	30.180	1.189	.324	.069	3.567	.299
	Lower-bound	90.539	1.000	90.539	1.189	.292	.069	1.189	.177
Device * Time * Fitness	Sphericity Assumed	108.895	3	36.298	1.430	.246	.082	4.290	.355
	Greenhouse-Geisser	108.895	2.702	40.302	1.430	.249	.082	3.864	.334
	Huynh-Feldt	108.895	3.000	36.298	1.430	.246	.082	4.290	.355
	Lower-bound	108.895	1.000	108.895	1.430	.249	.082	1.430	.203
Error(Device*Time)	Sphericity Assumed	1218.355	48	25.382					
	Greenhouse-Geisser	1218.355	43.232	28.182					
	Huynh-Feldt	1218.355	48.000	25.382					
	Lower-bound	1218.355	16.000	76.147					

a. Computed using alpha = .05

Tests of Between-Subjects Effects

Measure: MEASURE_1
Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	397.234	1	397.234	1.985	.178	.110
SEX	23.775	1	23.775	.119	.735	.007
Option	45.735	1	45.735	.229	.639	.014
Fitness	20.175	1	20.175	.101	.755	.006
Error	3202.225	16	200.139			

Pairwise Comparisons

Measure: MEASURE_1

(I) Device	(J) Device	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
1	2	.450	1.294	.733	-2.293	3.193
2	1	-.450	1.294	.733	-3.193	2.293

Based on estimated marginal means
a. Adjustment for multiple comparisons: Bonferroni.

Pairwise Comparisons

Measure: MEASURE_1

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[a]	
					Lower Bound	Upper Bound
1	2	.075	1.267	1.000	-3.738	3.888
	3	-.350	.923	1.000	-3.128	2.428
	4	-2.225	1.444	.857	-6.569	2.119
2	1	-.075	1.267	1.000	-3.888	3.738
	3	-.425	1.200	1.000	-4.034	3.184
	4	-2.300	1.284	.552	-6.161	1.561
3	1	.350	.923	1.000	-2.428	3.128
	2	.425	1.200	1.000	-3.184	4.034
	4	-1.875	1.037	.536	-4.994	1.244
4	1	2.225	1.444	.857	-2.119	6.569
	2	2.300	1.284	.552	-1.561	6.161
	3	1.875	1.037	.536	-1.244	4.994

Based on estimated marginal means
a. Adjustment for multiple comparisons: Bonferroni.

Appendix M: Rating of Perceived Exertion Results

Mauchly's Test of Sphericity[a]

Measure: MEASURE_1

Within Subjects Effect	Mauchly's W	Approx. Chi-Square	df	Sig.	Epsilon[b] Greenhouse-Geisser
Device	1.000	.000	0	.	1.000
Time	.716	4.914	5	.427	.814
Device * Time	.825	2.836	5	.726	.883

Tests of Within-Subjects Effects

Measure: MEASURE_1

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared	Noncent. Parameter	Observed Power[a]
Device	Sphericity Assumed	1.680	1	1.680	.514	.484	.031	.514	.104
	Greenhouse-Geisser	1.680	1.000	1.680	.514	.484	.031	.514	.104
	Huynh-Feldt	1.680	1.000	1.680	.514	.484	.031	.514	.104
	Lower-bound	1.680	1.000	1.680	.514	.484	.031	.514	.104
Device * SEX	Sphericity Assumed	4.524	1	4.524	1.385	.256	.080	1.385	.198
	Greenhouse-Geisser	4.524	1.000	4.524	1.385	.256	.080	1.385	.198
	Huynh-Feldt	4.524	1.000	4.524	1.385	.256	.080	1.385	.198
	Lower-bound	4.524	1.000	4.524	1.385	.256	.080	1.385	.198
Device * Option	Sphericity Assumed	.740	1	.740	.227	.640	.014	.227	.073
	Greenhouse-Geisser	.740	1.000	.740	.227	.640	.014	.227	.073
	Huynh-Feldt	.740	1.000	.740	.227	.640	.014	.227	.073
	Lower-bound	.740	1.000	.740	.227	.640	.014	.227	.073
Device * Fitness	Sphericity Assumed	.002	1	.002	.001	.982	.000	.001	.050
	Greenhouse-Geisser	.002	1.000	.002	.001	.982	.000	.001	.050
	Huynh-Feldt	.002	1.000	.002	.001	.982	.000	.001	.050
	Lower-bound	.002	1.000	.002	.001	.982	.000	.001	.050
Error(Device)	Sphericity Assumed	52.254	16	3.266					
	Greenhouse-Geisser	52.254	16.000	3.266					
	Huynh-Feldt	52.254	16.000	3.266					
	Lower-bound	52.254	16.000	3.266					
Time	Sphericity Assumed	9.523	3	3.174	4.811	.005	.231	14.433	.879
	Greenhouse-Geisser	9.523	2.442	3.900	4.811	.009	.231	11.749	.821
	Huynh-Feldt	9.523	3.000	3.174	4.811	.005	.231	14.433	.879
	Lower-bound	9.523	1.000	9.523	4.811	.043	.231	4.811	.540
Time * SEX	Sphericity Assumed	5.594	3	1.865	2.826	.048	.150	8.478	.643

	Greenhouse-Geisser	5.594	2.442	2.291	2.826	.061	.150	6.902	.576
	Huynh-Feldt	5.594	3.000	1.865	2.826	.048	.150	8.478	.643
	Lower-bound	5.594	1.000	5.594	2.826	.112	.150	2.826	.352
Time * Option	Sphericity Assumed	1.631	3	.544	.824	.487	.049	2.471	.215
	Greenhouse-Geisser	1.631	2.442	.668	.824	.467	.049	2.012	.195
	Huynh-Feldt	1.631	3.000	.544	.824	.487	.049	2.471	.215
	Lower-bound	1.631	1.000	1.631	.824	.378	.049	.824	.137
Time * Fitness	Sphericity Assumed	.197	3	.066	.100	.960	.006	.299	.067
	Greenhouse-Geisser	.197	2.442	.081	.100	.936	.006	.244	.065
	Huynh-Feldt	.197	3.000	.066	.100	.960	.006	.299	.067
	Lower-bound	.197	1.000	.197	.100	.756	.006	.100	.060
Error(Time)	Sphericity Assumed	31.671	48	.660					
	Greenhouse-Geisser	31.671	39.073	.811					
	Huynh-Feldt	31.671	48.000	.660					
	Lower-bound	31.671	16.000	1.979					
Device * Time	Sphericity Assumed	1.230	3	.410	.700	.557	.042	2.100	.187
	Greenhouse-Geisser	1.230	2.648	.464	.700	.540	.042	1.854	.177
	Huynh-Feldt	1.230	3.000	.410	.700	.557	.042	2.100	.187
	Lower-bound	1.230	1.000	1.230	.700	.415	.042	.700	.123
Device * Time * SEX	Sphericity Assumed	1.438	3	.479	.819	.490	.049	2.457	.214
	Greenhouse-Geisser	1.438	2.648	.543	.819	.478	.049	2.168	.201
	Huynh-Feldt	1.438	3.000	.479	.819	.490	.049	2.457	.214
	Lower-bound	1.438	1.000	1.438	.819	.379	.049	.819	.136
Device * Time * Option	Sphericity Assumed	2.799	3	.933	1.594	.203	.091	4.781	.393
	Greenhouse-Geisser	2.799	2.648	1.057	1.594	.209	.091	4.220	.365
	Huynh-Feldt	2.799	3.000	.933	1.594	.203	.091	4.781	.393
	Lower-bound	2.799	1.000	2.799	1.594	.225	.091	1.594	.221
Device * Time * Fitness	Sphericity Assumed	2.716	3	.905	1.546	.215	.088	4.639	.382
	Greenhouse-Geisser	2.716	2.648	1.026	1.546	.220	.088	4.095	.355
	Huynh-Feldt	2.716	3.000	.905	1.546	.215	.088	4.639	.382
	Lower-bound	2.716	1.000	2.716	1.546	.232	.088	1.546	.216
Error(Device*Time)	Sphericity Assumed	28.103	48	.585					
	Greenhouse-Geisser	28.103	42.370	.663					
	Huynh-Feldt	28.103	48.000	.585					
	Lower-bound	28.103	16.000	1.756					

a. Computed using alpha = .05

Tests of Between-Subjects Effects

Measure: MEASURE_1
Transformed Variable: Average

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Intercept	508.994	1	508.994	32.348	.000	.669
SEX	1.050	1	1.050	.067	.799	.004
Option	36.612	1	36.612	2.327	.147	.127
Fitness	79.651	1	79.651	5.062	.039	.240
Error	251.756	16	15.735			

Pairwise Comparisons

Measure: MEASURE_1

(I) Device	(J) Device	Mean Difference (I-J)	Std. Error	Sig.[a]	95% Confidence Interval for Difference[a] Lower Bound	Upper Bound
1	2	.337	.286	.255	-.268	.943
2	1	-.337	.286	.255	-.943	.268

Based on estimated marginal means
a. Adjustment for multiple comparisons: Bonferroni.

Pairwise Comparisons

Measure: MEASURE_1

(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	Sig.[b]	95% Confidence Interval for Difference[b] Lower Bound	Upper Bound
1	2	-.125	.165	1.000	-.621	.371
	3	-.700*	.172	.005	-1.217	-.183
	4	-.850*	.232	.012	-1.547	-.153
2	1	.125	.165	1.000	-.371	.621
	3	-.575*	.165	.018	-1.071	-.079
	4	-.725*	.184	.007	-1.279	-.171
3	1	.700*	.172	.005	.183	1.217
	2	.575*	.165	.018	.079	1.071
	4	-.150	.162	1.000	-.638	.338
4	1	.850*	.232	.012	.153	1.547
	2	.725*	.184	.007	.171	1.279
	3	.150	.162	1.000	-.338	.638

Based on estimated marginal means
*. The mean difference is significant at the .05 level.
b. Adjustment for multiple comparisons: Bonferroni.

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