Maximal Interval Handgrip Exercise For Blood Pressure Modification Among Post-Menopausal Women

by

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A thesis submitted in conformity with the requirements
for the degree of Doctor of Philosophy
Department of Exercise Sciences
University of Toronto

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Abstract

Handgrip (HG) exercise training reduces resting blood pressure (BP) but is infrequently employed. Common HG protocols prescribe sustained grips at moderate intensities of 20-50% of one’s maximum intensity, an approach that requires real-time force monitoring. This limits exercise accessibility, an especially important consideration for at-risk cohorts (ie. older women) who display low adherence to traditional aerobic exercise options.

This research describes the creation and evaluation of a novel HG strategy: the Maximal INTerval (MINT) strategy. MINT is highly accessible, easy to use, and participant-informed. Testing of acute cardiovascular responses to MINT among older women (n=20) with normotension demonstrated moderate BP increases during the exercise bout (systolic BP: 24 ± 3mmHg, diastolic BP: 11 ± 2) that swiftly returned to resting values following exercise cessation. In comparison to a commercially available strategy (ZONA), the MINT intervention took less time to complete and required less exercise effort, yet participants perceived greater exertion. Neither HG intervention produced post-exercise alterations to either resting forearm blood flow or peak reactive flow.

The concomitant creation of the MINT grip tool followed stages of new product development with structured focus groups (n=20). The result was a participant-preferred tool with a small grip circumference, slight grip contouring, soft foam covering, and black colour.
Finally, the MINT exercise protocol and MINT grip tool were combined and the impact of MINT HG training was assessed via measures of both exercise efficacy and exercise effectiveness. Among a cohort of post-menopausal women (n=17) with a range of resting BPs and various co-morbidities, eight weeks of MINT training effectively reduced resting systolic BP (128 ± 14mmHg to 122 ± 14mmHg), improved sample entropy (a measure of heart rate complexity) (1.36±0.10 to 1.62±0.11), and reduced cardiovascular reactivity to a serial subtraction stressor (21.7 ± 20.5mmHg to 19.0 ± 13.8mmHg).

Measures of adherence were high for this at-home handgrip training program (96.9%) with participants indicting high levels of both exercise effort and exercise enjoyment.

Collectively, the participant-informed MINT training strategy is a safe, efficacious, and effective exercise option for post-menopausal women to reduce resting blood pressure.
Acknowledgments

This thesis is dedicated to my husband, Chris, without your tremendous support and encouragement I would have never been able to put this all together. In life we need people who are not afraid to push us, ensuring that we never fall short of our dreams. Every day you push me to better and I will never settle for anything else than extraordinary; promise, promise.

This work is also dedicated to my family, the Bentley’s and the DeZorzi’s. In very different ways each one of you has provided me unwavering support. To my parents and brothers especially, thank you for your patience, your reinforcement, and for your understanding…from grade 1 through to grade 23!

Thank you to my research supervisor Scott Thomas. I have crazy ideas, ambitious goals, and emotions that follow roller coasters (at their best of times). You encouraged me to holistically develop myself as an academic and as a professional, reminding me constantly to not lose sight of my ultimate goal. Thank you for guiding me as I explored research questions that sometimes reached far beyond my limits.

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In conducting each of the described studies there were several people who were instrumental in making this research a success. The venous compliance software was written by Cathie Kessler. The arterial flow software was written by Dr. Jim. Duffin. Dr. Emma O’Donnell patiently provided training in pulse wave velocity and arterial augmentation. Dr. Sam Liu wrote the excel macro for data cleaning. Vanessa Dizonno diligently prepared recruitment materials and initiated study recruitment campaigns. Finally, Cindy Nguyen in her role of Research Assistant tirelessly stared at pages and pages of participant data. Cindy, it has been a true pleasure watching you develop as a researcher over these years and I hope to continue to hear about your inevitable success!

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<td>Acetylcholine</td>
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<td>AIX</td>
<td>Augmentation Index</td>
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<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
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<tr>
<td>ANS</td>
<td>Autonomic Nervous System</td>
</tr>
<tr>
<td>AO</td>
<td>Above Optimal Blood Pressure</td>
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<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<tr>
<td>BP</td>
<td>Blood Pressure</td>
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<tr>
<td>CCC</td>
<td>Cardiovascular Control Centre</td>
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<tr>
<td>crPWV</td>
<td>Carotid-radial Pulse Wave Velocity</td>
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<tr>
<td>CV</td>
<td>Cardiovascular</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular Disease</td>
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<tr>
<td>DBP</td>
<td>Diastolic Blood Pressure</td>
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<td>Epi</td>
<td>Epinephrine</td>
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<tr>
<td>EPR</td>
<td>Exercise Pressor Reflex</td>
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<tr>
<td>FBF</td>
<td>Forearm Blood Flow</td>
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<tr>
<td>FMD</td>
<td>Flow Mediated Dilation</td>
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<tr>
<td>HF</td>
<td>High Frequency</td>
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<tr>
<td>HG</td>
<td>Handgrip</td>
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<tr>
<td>HR</td>
<td>Heart Rate</td>
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<tr>
<td>HRV</td>
<td>Heart Rate Variability</td>
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<tr>
<td>HTN</td>
<td>Hypertension</td>
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<tr>
<td>JNC</td>
<td>United States Joint National Committee for Detection, Evaluation, and Treatment of High Blood Pressure</td>
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<tr>
<td>KT</td>
<td>Knowledge Translation</td>
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<td>KU</td>
<td>Knowledge User</td>
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<tr>
<td>LF</td>
<td>Low Frequency</td>
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<tr>
<td>MAP</td>
<td>Mean Arterial Pressure</td>
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<td>MINT</td>
<td>Maximal INTerval</td>
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<tr>
<td>MVC</td>
<td>Maximal Volitional Contraction</td>
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<tr>
<td>MSNA</td>
<td>Muscle Sympathetic Nerve Activity</td>
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<tr>
<td>NE</td>
<td>Norepinepinephrine</td>
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<tr>
<td>NO</td>
<td>Nitric Oxide</td>
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<tr>
<td>NS</td>
<td>Non-significant</td>
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<td>NT</td>
<td>Normotensive Blood Pressure</td>
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<td>Ratings of Perceived Exertion</td>
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<td>SBP</td>
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<td>SEM</td>
<td>Standard Error of the Mean</td>
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<td>SNS</td>
<td>Sympathetic Nervous System</td>
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<td>State Trait Anxiety Inventory</td>
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<tr>
<td>TTP</td>
<td>Time Tension Product</td>
</tr>
<tr>
<td>YLMP</td>
<td>Years Since Last Menstrual Period</td>
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<td>YLMP</td>
<td>Years Since Last Menstrual Period</td>
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CHAPTER 1

Introduction

1.1 Overview

Both patients and clinicians alike have expressed a strong desire for focused research dedicated to alternative treatment options, such as lifestyle interventions, for the management and improvement of one’s health. As a lifestyle intervention, handgrip (HG) exercise successfully reduces resting blood pressure (BP) ((Mean, [95%CI]) systolic BP (-6.8, -7.9 to -5.6mmHg) and diastolic BP (-4.0, -4.8 to -3.1mmHg)). Common HG training protocols prescribe sustained grip squeezes at low to moderate intensities of 20-50% maximal volitional contraction (MVC); an approach that requires real-time force outputs during each exercise bout to be regulated via either supervised laboratory visits and/or specialized at-home exercise equipment. Ultimately, this limits exercise accessibility greatly for the general population. Accessibility is especially important for particular at-risk cohorts, such as older women, who not only experience physiological declines attributed to the menopause transition, but who also display low adherence to traditional whole body aerobic exercise options.

The following studies describe the entire process of development, physiological assessment (acute and long-term), and behavioral assessment (exercise adherence and activity enjoyment) of a novel HG exercise strategy designed specifically for use among post-menopausal women. The Maximal INTerval (MINT) exercise strategy includes both the MINT handgrip exercise protocol and the MINT grip tool. The MINT strategy is highly accessible, easy to use, and participant-informed. Following a theoretical design strongly focused on the specific physiological responses of older women, the MINT exercise protocol was tested among women with various resting blood pressures to assess the acute cardiovascular responses both during the exercise bout and following exercise cessation. Occurring in parallel, the MINT grip tool was created following stages of new product development resulting in a final tool comprised of ideal design features, including a small grip circumference with slight grip contouring, soft foam covering, and black colour. Finally, the MINT exercise protocol and MINT grip tool were combined and the long-term impact of MINT handgrip training was assessed by evaluating both the exercise efficacy and exercise effectiveness. It was determined that eight weeks of MINT can effectively reduce resting systolic BP (127.5 ± 13.6mmHg to 122.4 ± 14.4mmHg, p<0.05) and improve heart rate complexity (1.36 ± 0.10 to 1.62 ± 0.11, p<0.05) in a cohort of older post-menopausal women with a range of resting blood pressures and various comorbidities. In addition to this noted exercise efficacy, adherence was high for
this at-home handgrip training program (96.9%) with participants indicating high levels of exercise enjoyment.

The overarching purpose of this research was to create a handgrip exercise option that was not only highly accessible and easy to follow, but that would also have a favorable training impact on the cardiovascular system (ie. resting BP reduction, improvements in vascular structure, shifts in neurocardiac control, etc.). Collectively, these studies indicate that high intensity interval grip training can be a safe and effective exercise strategy for at-home training among older post-menopausal women.

1.2 Organization of the Thesis

Following a review of the pertinent literature in Chapter 2, four distinct but connected studies are presented in chapters three to six. In the first study (Chapter 3), a within-participant randomized design with a control was used to examine the acute cardiovascular responses of post-menopausal women to two handgrip exercise protocols at two distinct time points: (1) the real-time responses of BP and heart rate are examined during a unilateral bout of handgrip exercise, and (2) the post-exercise recovery of blood pressure and heart rate are examined for thirty minutes following exercise cessation. The real-time and post-exercise responses are quantified and compared between three experimental visits: a moderate intensity design with sustained isometric grip contractions, a high intensity design with intermittent maximal grip contractions, and a comparative non-exercise control experimental visit.

In the second study (Chapter 4) the full design and initial evaluations of the Maximal INTerval handgrip exercise strategy are described. Part 1 of this research is dedicated to the MINT exercise protocol, beginning with the theoretically-driven conceptualization of a highly accessible exercise option for at-home exercise training that considers the unique physiological responses of older women to HG exercise. Part 2 of this research describes a product development opportunity that arose as a result of participant feedback from Part 1 that identified a need for a handgrip tool that would be better suited for maximal grip contractions. The creation of the MINT grip tool began with a mixed-methods assessment of participant opinions regarding two distinct in-laboratory grip tools. These qualitative and quantitative opinions informed the creation of four unique mock-MINT tools that were critiqued and compared against not only each other but also against the original two in-laboratory tools by structured focus groups. The end result of study two was the MINT exercise strategy, ready to be critically assessed for both efficacy and effectiveness.
In the third study (Chapter 5), a prospective cohort design was used to explore the physiological efficacy and behavioural effectiveness of the MINT exercise strategy. Physiological efficacy was explored by assessing the time course of cardiovascular alterations throughout an 8-week training intervention. Cardiovascular alterations of interest were resting systolic BP, diastolic BP, and HR. Additional physiological variables of interest include those that have been proposed as mediators of BP changes: a neurocardiac index of autonomic nervous control (heart rate variability (HRV)), indicators of arterial structure (radial augmentation index (AIx)), and carotid-radial pulse wave velocity (crPWV)). Behavioural effectiveness was explored by assessing at-home exercise adherence patterns, exercise enjoyment, and qualitative indicators of anticipated/actual barriers to exercise.

In the fourth and final study (Chapter 6), a prospective cohort design was used to explore the inter-individual variability of handgrip-induced training responses using cardiovascular reactivity. Not only is the potential for one’s cardiovascular reactivity to predict future training-induced blood pressure reductions determined, but the ability of MINT exercise training to lower one’s reactivity to psychophysiological stressors was also examined.

In the final chapter (Chapter 7), the hypotheses are revisited in a unifying discussion that summarizes the key observations of each study, providing a critical interpretation of the collective findings with suggestions for future research.

### 1.3 Experimental Hypotheses and Purposes

#### 1.3.1 Study One: In Study one (Chapter 3), entitled ‘A Direct Comparison of the Instantaneous and Post-Exercise Cardiovascular Responses to Two Handgrip Exercise Designs: a high intensity interval design and a moderate intensity sustained design’, the research objectives were:

1. To characterize and compare the instantaneous cardiovascular responses of blood pressure and heart rate during the two exercise designs. **Hypothesis:** both handgrip exercise designs will instantaneously drive systolic and diastolic BP, with greater values associated with the high intensity design.

2. To characterize and compare the post-exercise cardiovascular recovery of blood pressure and heart rate for thirty minutes following exercise cessation. **Hypothesis:** despite augmented instantaneous cardiovascular responses, high intensity handgrip exercise will promote a more rapid return of systolic and diastolic BP to day-of-resting values.

3. To compare the sustained influences of handgrip exercise design on resting and peak forearm
blood flow. **Hypothesis:** as compared to a non-exercise control, following both handgrip exercise protocols there will be augmentations to resting forearm blood flow without differences in peak reactive hyperaemic flow.

1.3.2 **Study Two:** In Study two (Chapter 4), entitled ‘The Design and Comprehensive Evaluation of Both an Exercise Protocol and a Handgrip Tool for use as the Maximal INTerval (MINT) Handgrip Training Strategy’, the research is broken into two distinct segments. The primary objectives of Part 1, dedicated to the MINT exercise protocol, were:

1. To describe the theoretically driven conceptualization of a highly accessible exercise option for at-home exercise training that considers the unique physiological responses of older women to handgrip exercise.
2. To experimentally analyze the MINT exercise protocol by quantifying participant grip performance, describing the acute cardiovascular responses and collective participant feedback.

The primary objectives of Part 2, dedicated to the MINT grip tool, were:

1. To describe and isolate relevant items of participant feedback regarding the two in-laboratory handgrip devices for the subsequent construction of four unique grip tools.
2. To gather participant evaluations of all six grip tools through focus groups.

1.3.3 **Study Three:** In Study three (Chapter 5), entitled ‘Maximal Interval Handgrip Exercise Training Lowers Resting Blood Pressure and Increases Heart Rate Complexity among Older Women’, the primary research objectives with corresponding hypotheses were:

1. To explore the physiological **efficacy** of MINT handgrip exercise training by assessing cardiovascular adaptations (resting SBP, DBP, and HR) as a result of an 8-week training intervention. **Hypothesis:** high intensity handgrip exercise training will cause reductions to resting blood pressure but not heart rate.
2. To explore indicators of behavioural **effectiveness** including at-home exercise adherence patterns, activity enjoyment, and qualitative indicators of anticipated versus actual barriers to exercise. **Hypothesis:** although participants would anticipate barriers of ‘time’ and ‘habit’, they would none the less demonstrate high exercise adherence to MINT exercise.
3. To explore adaptations to proposed mediators of blood pressure reductions, including a neuro-cardiac index of autonomic nervous control (heart rate variability) and indicators of arterial structure (radial augmentation index and carotid-radial pulse wave velocity). **Hypothesis:** eight weeks of handgrip training will result in shifts to neurocardiac measures that align with
parasympathetic predominance while indices of arterial structure will remain unchanged.

1.3.4 Study Four: In Study four (Chapter 6), entitled ‘Examining the Relationship Between Cardiovascular Reactivity and Resting Blood Pressure Reductions Following Handgrip Training in Post-Menopausal Women’, the primary research objectives with corresponding hypotheses were:

1. To investigate if cardiovascular stress reactivity responses to psychophysiological stressors are predictive of handgrip-induced training reductions in systolic blood pressure. **Hypothesis:** cardiovascular reactivity to a serial subtraction stressor and a handgrip stressor would predict training reductions.

2. To investigate if high intensity intermittent handgrip training attenuates cardiovascular reactivity to psychophysiological stressors. **Hypothesis:** exercise training will elicit similar attenuations of cardiovascular reactivity to both a serial subtraction stressor and a handgrip stressor.
CHAPTER 2
Review of Literature

Cardiovascular (CV) disease is the number one cause of death worldwide, representing nearly one-third (31%) of global deaths in 2012 (World Health Organization, 2013a). There are strong independent correlations among CV disease morbidity, CV disease mortality, and high resting blood pressure (Cornelissen, Fagard, Coeckelberghs & Vanhees, 2011), with more than 50% of all CV diseases directly related to high BP (World Health Organization (2013a). Health strategies and lifestyle modifications, such as exercise, which focus on the establishment and maintenance of optimal resting BP levels are critical in order to reduce the growing global burden of CV disease (World Health Organization, 2013b).

2.1 Resting Blood Pressure and Cardiovascular Disease

Resting BP is organized into sequential categories in order to help identify individuals who are at-risk for future development of hypertension (HTN) and to facilitate therapeutic treatments (Table 2.1). Both the Canadian Hypertension Education Program (Dasgupta et al., 2014) and the United States Joint National Committee for Detection, Evaluation and Treatment of High BP (JNC) (Chobanian et al., 2003) have identified that optimal resting BP should be a systolic BP <120mmHg and a diastolic BP <80mmHg. Alternatively, HTN is when high systolic (≥140 mmHg) and/or diastolic BP (≥90mmHg) is recorded at two or more physician visits. Hypertension is considered a chronic vascular condition with stages 1 and 2 as the most common forms (Dasgupta et al., 2014). The clinical diagnosis of HTN currently affects one in four adults globally and the incidence is expected to increase by 60% between 2000 and 2025 (Campbell & Chen, 2010). In Canada specifically, it is estimated that approximately one in five Canadian adults have HTN (Wilkins et al., 2010).

<table>
<thead>
<tr>
<th>Category</th>
<th>Systolic BP (mmHg)</th>
<th>Diastolic BP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Normal</td>
<td>120-129</td>
<td>80-84</td>
</tr>
<tr>
<td>High Normal</td>
<td>130-139</td>
<td>85-59</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>Stage 2</td>
<td>160-179</td>
<td>100-109</td>
</tr>
<tr>
<td>Stage 3</td>
<td>180-209</td>
<td>110-119</td>
</tr>
<tr>
<td>Stage 4</td>
<td>≥210</td>
<td>≥120</td>
</tr>
</tbody>
</table>

Table 2.1 Classification of Blood Pressure for Adults Age 18 years and Older
During the progressive rise in arterial BP away from optimal and toward HTN a transitional stage is passed. This stage, quantitatively expressed as 120-139/80-89 mmHg, is called pre-hypertension (pre-HTN) (Chobanian et al., 2011). The original objective of the JNC in segmenting pre-HTN was to increase awareness about the importance of identifying individuals who would benefit from the adoption of healthy lifestyles. Analyses focused on the pre-HTN stage have revealed important health considerations. In the Framingham Heart Study pre-HTN, particularly the subclass of high-normal BP (130-139/85-89 mmHg), was associated with an increased incidence of CV diseases such as myocardial infarction and coronary artery disease (Qureshi, Suri, Kirmani, & Divani, 2005; Vasan et al., 2001). An analysis from the Women’s Health Initiative, that included 60,785 post-menopausal women, identified pre-HTN to be associated with an even wider spectrum of CV disease, including myocardial infarction, stroke, hospitalized heart failure, any cardiovascular event, and cardiovascular death (Hsia et al., 2007). In the MONICA study, participants who transitioned from normotension to the upper levels of pre-HTN had a similar increase in risk of CV events ([Hazard Ratio, 95%CI] 1.6, 1.1 to 2.3) to those who progressed from the lower level of pre-HTN to the HTN range (1.6, 1.2 to 2.3) (Hansen et al., 2007).

The stage of pre-HTN is an imperative point in disease progression where the initiation of effective treatments can be especially impactful. Historically, this early detection and treatment of high BP, including pre-HTN, has been dismal. National surveys conducted in the late 1980s and early1990s found that when compared to Americans, Canadians were less likely to be aware of their high BP, less likely to be formally diagnosed, and less likely to seek treatment (Campbell & Chen, 2010). As a result of this initial discrepancy the national strategic plan for hypertension prevention and control was developed (Chockalingam et al., 2000), followed by a knowledge translation program for health care professionals (Canadian Hypertension Education Plan) (Zarnke et al., 2000). These initiatives have been very successful as the treatment and control of high BP has increased nearly fivefold, from 12% to 66% in Ontario alone (Leenen et al., 2008).

Within pre-HTN BP classification, lifestyle modifications have been consistently documented as an effective, non-pharmaceutical strategy for BP control (Pimenta & Oparil, 2010). Some of the most impactful lifestyle modifications include weight loss, dietary alterations and exercise. Determining accessible, feasible and effective options for lowering BP is one way of reducing the Canadian, and global, burden of CV disease morbidity and mortality.
2.2 Cardiovascular Disease and the Impact of Age and Sex

In addition to the direct impact of high resting BP, the risk of developing CV disease (CVD) is also influenced by the non-modifiable risk factors of age and sex. Men will typically present with CVD 10 years earlier than women with a greater number and severity of CV risk factors (Anand et al., 2008). As women age there is an exponential increase in CVD around the age of 55–60 years suggesting that menopause may augment CVD risk (Schenck-Gustafsson, 2009). The interaction of age and sex is most strikingly highlighted among Canadian women when considering that the relative-risk of developing CVD increases fourfold after the menopause transition (Yang & Reckelhoff, 2011).

The menopause transition is the natural reduction (perimenopause) and then loss (menopause) of circulating endogenous estrogens resulting in the loss of both menstrual bleeding and ovarian ovulation. Although natural menopause in women can be affected by a variety of factors such as ethnicity, diet, physical activity, and genetics (Gold, 2011), the average age that women experience the menopause event is 51 years with the normal range from 40 to 60 years of age (National Institute on Aging, 2013; Shaw & Shaw, 2009). At this time there is a concomitant elevation in the incidence of diagnosed HTN with resulting prevalence rates higher for women (77.02 per 1000 people) as compared to men (74.57 per 1000 people) following the 6th decade of life (Public Health Agency of Canada, 2010).

The disparity in CV disease incidence between aged men and women is now recognized worldwide with the European Society of Cardiology formally publishing public policy documents (Stramba-Badiale et al., 2006) and the American Heart Association publishing separate guidelines for CVD prevention for both men and women (Mosca et al., 2004; Mosca et al., 2007; Mosca et al., 2011). Given the undeniable correlation between CVD and high BP, especially among aging women, the remainder of this literature review will focus on BP and the physiological factors related to its control. Alterations to resting BP must involve one (or both) factors that determine mean arterial blood pressure: cardiac output and total peripheral resistance. In exploring these two factors, this review will highlight vascular health (and the direct link to HTN) and autonomic nervous health (and the direct influence on BP control).

2.3 Blood Pressure and Vascular Health

In addition to the strong relationship between BP and CVD, there is also a direct link between BP and assessments of vascular health, including assessments of arterial structure, arterial function, and venous function.
2.3.1 Measures of Arterial Structure: Large conduit arteries are compliant vessels that buffer pressure changes resulting from intermittent ventricular ejection of blood into systemic circulation. Vessels that have great elasticity, such as the aorta, have the ability to distend and recoil favorably, described as the Windkessel effect of arteries (Belz, 1995). Pressure waves within the vessels are reflected back from the periphery and summate with the forward-progressing wave producing a characteristic pressure waveform that can be visualized and numerically analyzed. With arterial stiffening the speed of blood pressure waves along a vessel (Pulse Wave Velocity (PWV)) increases, resulting in modified shape characteristics of the resulting waveform (Augmentation Index ((AIx) changes (Wilkinson et al., 1998). The measurements of PWV and AIx can be non-invasively acquired using the SphygmoCor™ system and applanation tonometry to accurately record peripheral arterial waveforms from the radial, carotid, and/or femoral arteries (O’Rourke & Gallagher, 1996). This system uses a validated integral transfer function to calculate the central aortic waveform and the augmentation index (AIx) (an index of arterial distensibility). Applanation tonometry is a reliable (Currie, Thomas, & Goodman, 2009), reproducible (Papaioannou et al., 2004), non-invasive, and easily applied technique to measure PWV and AIx as indices of arterial stiffness (Wilkinson et al., 1998). Within the aged population, elevated measures of carotid-femoral PWV are associated with high mean arterial blood pressure (MAP), diabetes, increased age and female sex, such that: PWV = -5.88 + 0.07(MAP)(mmHg) + 2.36 (diabetes)(0=no, 1=yes) + 0.14 (age)(years) -0.72(sex)(1=man, 2= woman) (Alecu et al., 2006).

2.3.2 Measures of Arterial Function: The technique of flow-mediated dilation (FMD) is a non-invasive approach to examine vasodilator function in vivo (Thijssen et al., 2011). FMD is widely believed to reflect endothelium-dependent nitric oxide (NO)-mediated arterial function. It has even been argued that FMD provides independent prognostic information which may exceed the predictive value of traditional risk factors (Thijssen et al., 2011). Although this prognostic value may be diminished in older individuals with limited arterial distensibility (Witte et al., 2005; Yeboah et al., 2009), previous research has noted strong associations between FMD and coronary events (Rossi, Nuzzo, Origliani, & Modena, 2008).

The technique of FMD involves high-resolution B-mode ultrasound equipment for detecting conduit artery edges (for measuring diameter) and a Doppler beam aperture for the determination of blood flow velocity (Thijssen et al., 2011). Research in the past two decades of FMD use has become quite heterogeneous, with deviations from the original technique described by Celermajer and colleagues in 1994. One such deviation includes brachial artery reactivity, a measure of the increase in brachial artery
diameter in response to flow mediated shear stress induced by the release of an occlusion cuff (Rubenfire, Cao, Smith, & Mosca, 2000). The typical occlusion technique involves the inflation of a brachial cuff to 50 mmHg above resting systolic blood pressure for 10 minutes, followed by the rapid release of the cuff (Corretti, Plotnick, & Vogel, 1995). This reactivity has been inversely associated with coronary risk factors and overall arterial health (Celemajer, Sorensen, Bull, Robinson, & Deanfield, 1994). Previous research examining the impact of unilateral handgrip training exercise has reported only localized improvements in FMD among medicated hypertensives (McGowan et al., 2007a) but not among normotensives (McGowan, Levy, McCartney, & MacDonald, 2007). Localized improvements were confirmed following four weeks of unilateral exercise program in a population of older men (73-90 yrs) who experienced a 45% improvement in brachial artery reactivity in the training arm only. As an alternative to the occlusion-induced brachial reactivity technique, researchers have found that 120 seconds of an isometric handgrip contraction held at 33% of peak force elicits a comparable brachial reaction and is also strongly associated with coronary risk factors (Rubenfire et al., 2000).

A major drawback to completing brachial reactivity following occlusion is that this assessment only provides information regarding conduit artery function. To acquire a more comprehensive representation of arterial vascular function in a localized area, resistance vessels can be included in the assessment by conducting strain-gauge plethysmography with reactive hyperemia; a validated and reproducible non-invasive technique (Higashi et al., 2001; Tousoulis, Anteniades, & Stefanadis, 2005). To complete this assessment resting forearm blood flow (FBF) is compared to reactive hyperaemic forearm blood flow (RHFB) and the difference is expressed as a change score in mL/min/mL of tissue.

Resting FBF is determined by calculating the average forearm flow using three bouts of venous occlusion (10 sec @ ~50 mmHg) separated by rest (5 sec @ 0 mmHg). Changes in forearm girth, representing overall FBF, are measured using a mercury-in-Silastic strain-gauge plethysmograph (Sinoway et al., 1987). As a reference, older women have normal FBF values in the range of 3.2 to 3.3 mL/min/100mL (Rossow et al., 2014) with slightly higher blood flow in older pre-menopausal women 3.6 mL/min/100mL (Kingsley & Figueroa, 2012). RHFB is determined by calculating the increase in blood flow following five minutes of full arm arterial occlusion (at ~200 mmHg), a technique that allows for the endothelial function of smaller resistance arterioles to be included in the forearm vascular analysis. Normal RHFB values in older women have been reported in the range of ~22.6 mL/min/100mL (Rossow et al., 2014). Whole body resistance training programs improve RHFB among aged ([pre to post], 22.6 to 26.7 mL/min/100mL) but not young (21.7 to 21.4 mL/min/100mL) women (Rossow et al., 2014). However, young women showed favorable modifications to RHFB following eight weeks of handgrip (HG).
exercise training of either 3 days/wk of training (26 to 36 mL/min/100mL) or 5 days/wk of training (26 to 38 mL/min/100mL) (Badrov et al., 2013a). It has yet to be determined if handgrip exercise, acutely or chronically, directly impacts the vasculature of older post-menopausal women.

2.3.3 Measures of Venous Function: Considering that two-thirds (or ~70%) of the blood volume is located within the venous vessels, small changes to the venous bed can greatly impact blood pressure control (Lindenberger & Lanne, 2007; Rothe 1983). However, research regarding the venous compliance of humans with elevated BP has shown mixed results, with some reporting decreased peripheral venous compliance (London et al., 1978; Takeshita & Mark, 1979) and others concluding no change (Houston, Fernandez, & Snedden, 1985; Wood, 1961). Altogether, increased autonomic reactivity exhibited in HTN has been postulated as the underlying mechanism behind alterations in venous compliance seen in HTN (Delaney, Youngm Disabatino, Stillabower, & Farquhar, 2008).

Halliwill et al. developed and validated a non-invasive technique for measuring venous function (Halliwill, Minson, & Joyner, 1999). The technique involves mercury-in-Silastic strain gauge plethysmography (similar to the technique for arterial function) with different cuff pressures and inflation/deflation timing. A brachial limb cuff is rapidly inflated to 60mmHg (to occlude venous outflow with maintained arterial inflow) and held for 8 minutes. At the end of the 8-min inflation period, the cuff is deflated at a rate of 1mmHg/s for 60s (until 0 mmHg). Data extraction and subsequent quantification of results follow the original quadratic regression equation described by Halliwill et al. such that

$$\Delta\text{Limb Volume} = \beta_0 + \beta_1 \cdot (\text{cuff pressure}) + \beta_2 \cdot (\text{cuff pressure})^2$$

where $\beta_0$ is a lumped variable indexing venous capacitance, and Venous Compliance $= \beta_1 + \beta_2 \cdot (\text{cuff pressure})$.

A direct comparison of young, age-matched cohorts of men and women revealed that venous compliance is lower in both normally menstruating women (26%) and oral contraceptive users (~19%) when compared to young men (Meendering, Torgrimson, Houghton, Halliwill, & Minson, 2005). At low transmural pressures men have significantly greater venous compliance. As transmural pressures increase the sex-dependent difference in compliance disappears. Interestingly, the sex-dependent difference in venous compliance is diminished if the contribution of capillary filtration is accounted for (Lindenberger & Lanne, 2007). It is speculated that the capillary filtration of vessels and the resulting interstitial fluid accumulation are partially dependent on circulating estrogens. However, although changes in venous compliance follow along with cycles of low and high estrogen the resulting differences are insignificant. It is currently unclear if the rise in resting BP and cardiovascular disease in post-menopausal women is
correlated with the dramatic reduction in circulating estrogens and their potential influence on venous compliance.

2.3.4 Additional Impact of Menopause on the Vasculature: Rationale for the dramatic rise in resting BP has been attributed, in part, to the loss of physiologically beneficial endogenous estrogens. Estrogens, specifically 17β-estradiol, are cardioprotective among pre-menopausal women. By activating both α- and β-estrogen receptors, 17β-estradiol inhibits smooth muscle cell proliferation and fibrosis (including vascular smooth muscle), attenuates atherosclerotic plaque progression, and aids in the re-endothelization of injured vasculature (Yang & Reckelhoff, 2011). 17β-estradiol also directly impacts the vasculature locally by potentiating endothelium-dependent vasodilator responses, including the rapid non-genomic increase in NO production and bioavailability (O’Donnell, Goodman, & Harvey, 2011). Nitric oxide is the most important protective molecule in the vasculature, regulating vascular tone, inhibiting vascular smooth muscle cell proliferation, inducing cellular apoptosis, attenuating platelet aggregation, and reducing cellular adhesion to vascular walls (O’Donnell et al., 2011). Therefore, the loss of endogenous estrogens has a profound impact on vasculature in post-menopausal women.

2.4 Physiological Control of Blood Pressure

Arterial BP is controlled simultaneously by numerous integrated components including neural control, local control, and hormonal control. Conceptually, BP is monitored by an adaptive control system with three components: afferent input, control centre, efferent output. The control centre, located within the dorsal region of the medulla oblongata, is constantly comparing actual BP against a pre-determined set-point. If there is a discrepancy in this comparison that BP is adjusted using efferent signals to the heart (to alter heart rate and cardiac output), to the blood vessels (to alter vascular tone), to the kidneys (to alter fluid excretion), and to the adrenal glands (to alter hormone production/secretion). As the efferent pathways effectively elicit change, BP measures are communicated via afferent signals to the cardiovascular regulatory centre. The cycle of afferent detection, control centre modulation, and efferent effects is constantly adjusted to meet any demands placed on the CV system (Levy & Pappano, 2007). Short-term BP adjustments are made predominantly through the baroreceptor afferents and efferents to the heart and blood vessels. Long-term adjustments are made predominantly through efferents to the kidneys and adrenal glands (Guyton & Hall, 2000).

2.4.1 Neural Control of Blood Pressure: During a single bout of exercise, dynamic or static, there are cardiovascular and hemodynamic adjustments that are made to meet the metabolic demands of working
skeletal muscle (Fadel & Raven, 2012). These demands are in part met by precise alterations directed by the autonomic nervous system. For example, BP is adjusted by increasing sympathetic influence and withdrawing parasympathetic influence via three distinct neural mechanisms: Central Command, Exercise Pressor Reflex, and the Baroreflex (Arterial and Cardiopulmonary) (Fadel & Raven, 2012; Murphy, Mizuno, Mitchell, & Smith, 2011).

Central Command is a feed-forward mechanism that transmits excitatory inputs to both descending motor efferents from the cerebral cortex and to cardiovascular control circuits within the medulla oblongata of the brainstem (Murphy et al., 2011; Williamson, McColl, Mathews, Mitchell, Raven, & Morgan, 2002). When the cardiovascular control centre (CCC) is stimulated by the volitional intent to exercise, the activity of the autonomic nervous system (ANS) is altered through its two distinct branches; sympathetic (SNS) and parasympathetic (PNS). The SNS typically raises BP through predominantly cardiostimulatory (increasing heart rate and stroke volume) and vasculostimulatory (increasing total peripheral resistance) actions, while the PNS reduces BP by reducing heart rate, stroke volume, and total peripheral resistance (Guyton & Hall, 2000). The influence of central command is independent of exercise intensity or actual force production and has instead been linked to ratings of perceived exercise exertion (Williamson, Fadel, & Mitchell, 2006); a link that could have implications when considering the anticipation of an exercise bout that was previously perceived to be difficult.

Another component of the neural control of BP that is involved in the control of BP during bouts of exercise is the Exercise Pressor Reflex (Kaufman & Hayes, 2002). This reflex is comprised of two groups of thin fiber sensory nerves that ultimately affect ANS outflow from central locations (Alam & Smirk, 1937; Fernades et al., 1990; Freund, Rowell, Murphy, Hobbs, & Butler, 1979; Iellamo et al., 1999). The two groups of fibers independently participate in the muscle mechanoreflex (group III fibers) and the muscle metaboreflex (group IV fibers). Group III fibers (thinly myelinated, Aδ fibers) are rapidly stimulated by mechanical distortion of receptors located on unencapsulated nerve endings and pacinian corpuscles (Kaufman & Hayes, 2002; Murphy et al., 2011). Group IV fibers (unmyelinated, C fibers) are stimulated by the chemical milieu of skeletal muscle resulting from the accumulation of metabolites such as potassium, lactic acid, bradykinin, and adenosine (Kaufman & Hayes, 2002; Murphy et al., 2011). It is well known that isometric muscular contractions of >30% MVC result in diminished blood flow to the muscle body, yielding an accumulation of metabolites and an increased activation of the metaboreflex (Rowell, 1993). Quantification of cardiovascular outputs as a result of the metaboreflex activation has yet to be compared between the sexes in older individuals.
Finally, the Baroreflex (Arterial and Cardiopulmonary) controls BP by sensing the vascular environment and comparing it to a predetermined set-point. The arterial baroreflex is a negative feedback loop that modulates beat-to-beat variations in BP by continually adjusting heart rate, stroke volume, and total peripheral resistance. Blood pressure is monitored via arterial baroreceptors. These are unencapsulated free nerve endings located at the medial-adventitial vascular border of both the carotid sinuses and the aortic arch (Fadel & Raven, 2012) that detect stretch and deformation of the arterial wall as it relates to changes in pulse pressure (Dampney et al., 2002). The baroreceptors can sense pressure changes over a span of ~50-180mmHg and transmit information to the nucleus tractus solitarii of the CCC (medulla oblongata) for fast integration and modulation of ANS output (Fadel & Raven, 2012).

In an attempt to understand the complex role of the arterial baroreflex during exercise, Melcher and Donald constructed full stimulus-response curves of isolated carotid baroreceptors in chronically instrumented exercising dogs (Melcher & Donald, 1981). The resetting of the arterial baroreflex set-point was later confirmed in humans by Potts et al. as they described an upward and rightward shift of the stimulus-response curve with the preservation of reflex gain that has been positively correlated with exercise intensity (Chen & Bonham, 2010; Fadel & Raven, 2012; Kimmerly, Wong, Salzer, Menon, & Shoemaker, 2007; Ogoh et al., 2003; Potts, Shi, & Raven, 1993).

The arterial baroreflex is also considered one of the potential mechanisms leading to post-exercise reductions in blood pressure. In this case the operational set-point is reset to defend a lower than resting BP. Skeletal muscle afferents which communicate with the nucleus tractus solitari release substance P at neurokinin-1 receptors on GABAergic interneurons which are partly responsible for the re-setting of the operational setpoint to values above resting during exercise and below resting during the post-exercise recovery period (Collins & DiCarlo, 1993; Halliwell, Taylor, & Eckberg, 1996). As a result of this lower operational setpoint there are reductions in sympathetic outflow from the CCC (Chen & Bonham, 2010; Halliwill et al., 2013; Kimmerly et al., 2007).

In addition to the arterial baroreflex, there is building evidence that the cardiopulmonary baroreceptors also play an important role in the neural control of cardiovascular responses to exercise. The cardiopulmonary baroreceptors are low-pressure mechanically sensitive stretch receptors that are found within structures of the thorax, such as the heart, the great veins, pulmonary arteries, and pulmonary veins. Elevation in central volume, or central pressure, increases vagal afferent nerve firing ultimately decreasing sympathetic outflow. The role of the cardiopulmonary reflex during HG exercise needs to be further investigated.
There is a complicated interaction between all of these mechanisms of cardiovascular control during a single bout of exercise. There is strong experimental support for the idea that both activation of skeletal muscle afferents and central command can reset the arterial baroreflex (McIlveen, Hayes, & Kaufman, 2001). Furthermore, with strong stimulation of skeletal muscle afferents the sympathetic activation is buffered by the arterial baroreflex. Therefore, much larger pressor responses are observed after baroreflex denervation (Sheriff, O’Leary, Scher, & Rowell, 19990; Waldrop & Mitchell, 1985).

It is necessary to consider that all three of these components (ie Central Command, Exercise Pressor Reflex, and the Baroreflex (Arterial and Cardiopulmonary)) work together to integrate control of the entire cardiovascular system in unison. These interactions remain to be fully elucidated especially as they pertain to post-menopausal women.

2.4.1.1 Neural Control of Blood Pressure and The Impact of Age and Sex: With advancing age women experience sex-specific changes to the autonomic nervous control of BP, an additional factor that contributes to the rise in resting BP. Specifically within a population of young women (<40 years), the sympathetic influence directly contributing to BP is lower than age matched young men. As women age the sympathetic influence directly contributing to BP becomes stronger and eventually surpasses that of older men (Joyner, Charkoudian, & Wallin, 2010). The shift in neurocardiovascular control may contribute to post-menopausal increases in CV risk. At younger ages men have a greater whole body SNS activity than women as demonstrated with various measurement techniques including plasma NE levels (< in women), muscle sympathetic nerve activity (MSNA) recordings (<in women), and the heart rate variability assessment of LF/HF power ratio (< in women). In young women, the reduced SNS effect on the vasculature is evident since their vasculature is less responsive to adrenergic stimuli such as infused NE. This reduced responsiveness is thought to be the result of enhanced β-receptor stimulation in younger pre-menopausal women (Joyner et al., 2010). With younger women, all autonomic nervous recordings fluctuate with the menstrual cycle, with greater sympathetic tone during the mid-luteal phase (low estrogens) of the ovarian cycle (Dart, Du, & Kingwell, 2002).

Overall, young women display lower sympathetic support of BP regulation (Christou et al., 2005) with a concomitant blunted vasoconstrictor response (Kneale, Chowienczyk, Brett, Coltart, & Ritter, 2000). Following menopause there is a shift in this autonomic influence, with a decrease in vagal tone modulation with preserved sympathetic tone resulting in the predominance of sympathetic activity. This shift is exemplified through measures of heart rate variability and an increase in the LF/HF ratio.
Increasing age in women is also associated with a decrease in β-adrenoreceptor responsiveness, an increase in α1-adrenoreceptor responsiveness, and impaired baroreceptor sensitivity (Lavi et al., 2007).

The dominance of sympathetic activity systemically may be one of the reasons for the increased CV risk following the menopausal shift (Lavi et al., 2007). Finding appropriate, non-invasive ways of reducing SNS tone may help mediate some of the increased CV risk.

2.4.2 Local Control of Blood Pressure: Locally, arterial BP can be controlled through the production and/or release of vasoactive compounds from sites within the cardiovascular system. These compounds will influence the vascular smooth muscles that surround resistance arterioles and result in alterations to blood flow in order to match the metabolic demands of a specific tissue. The predominant local vasodilators are potassium, NO, prostacyclin, and adenosine while the predominant local vasoconstrictor is endothelin1. Specific details pertaining to the local effects of NO were discussed in section 2.3.3 (in relation to FMD) and will be discussed in section 2.4.3 (in relation to effects of estrogens).

2.4.3 Hormonal Control of Blood Pressure: There are numerous hormones involved in the regulation of arterial BP, including catecholamines, renin, aldosterone, vasopression, and atrial natriuretic peptide (Chopra, Baby, & Jacob, 2011).

**Norepinephrine (NE):** NE is an SNS associated hormone (in this case a neurotransmitter) that is released from the synaptic endings of SNS neurons on peripheral vasculature. The released NE activates post-synaptic α1-adrenergic receptors and results in vasoconstriction through contraction of the vascular smooth muscle. During this process there are excess amounts of NE released in order to ensure the target tissue vasoconstriction. This excess NE stimulates α2-receptors located on the pre-synaptic nerve ending resulting in termination of NE release through negative feedback (Chopra et al., 2011).

**Epinephrine (Epi):** Epi is an SNS associated hormone predominantly released into the blood by the adrenal glands. Due to its widespread distribution the effects of Epi can be found throughout the body as it is recognized by both α and β-adrenergic receptors. Activation of β-receptors within the heart enhances cardiac function via improved contractility and increased HR. This ultimately increases arterial BP through increased cardiac output (Chopra et al., 2011). Activation of α1-receptors within the vasculature causes vascular smooth muscle contraction and potent vasoconstriction. Alternatively, activation of vascular β-receptors causes modulation to intracellular calcium concentrations, resulting in vasodilation in regions such as the working skeletal muscle (Guyton & Hall, 2000; Levy & Pappano, 2007).
**Acetylcholine (Ach):** Ach is a PNS associated hormone (in this case a neurotransmitter) that is released from the synaptic endings of PNS neurons on peripheral vasculature. The released Ach activates muscarinic receptors and results in vasodilation (Guyton & Hall, 2000) only in the cranial and sacral regions (Levy & Pappano, 2007). However, the effects of Ach on BP are minimal. Within the heart, Ach directly activates muscarinic receptors on the myocardium, reducing contractility and diastolic filling time. In addition, Ach will hyperpolarize the spontaneously depolarizing clusters of autonomic cells within the sinoatrial and atrioventricular nodes. The resulting change in membrane potential effectively slows heart rate, reducing cardiac output and decreasing arterial BP (Guyton & Hall, 2000).

**Additional Hormones of Blood Pressure Control:** Non-nervous system hormones contributing to BP regulation include the Renin-Angiotensin-Aldosterone System. Angiotensin II is not only a potent vasoconstrictor (Hillaert et al., 2011), it also increases blood volume by causing the release of aldosterone and the subsequent reabsorption of sodium and water in the kidneys. With similar effects to angiotensin II, vasopressin (aka, anti-diuretic hormone) also increases blood volume via water reabsorption and is a powerful vasoconstrictor. Atrial natriuretic peptide is released from the cardiac atria in response to high blood volume. Atrial natriuretic peptide initiates vasodilation in the peripheral vasculature (Ogedegbe et al., 2008), reduces aldosterone excretion from the adrenal glands (Potter, Yoder, Flora, Antos, & Dickey, 2009), and reduces vascular SNS activation in the peripheral vasculature (Potter et al., 2009).

**Estrogens:** Systolic blood pressure increases with advancing age in both men and women. Prior to the age of 60, the slope of this SBP increase is steeper among men. After age 60 this pattern switches and there is now a more dramatic rise in SBP with age among women. This trend mirrors hypertension patterns, with the prevalence of hypertension higher in older women than age matched men (Masi, Hawkley, Xu, Veenstra, & Cacioppo, 2009). Systolic BP trends over the lifecycle are consistent with age- and sex-related differences in 17β-estradiol production, a hormone with known vasodilatory effects (Masi et al., 2009).

Through its influence on NO, estrogen can bring about changes to arterial resting tone either genomically (increased endothelial NO synthase expression) or nongenomically (increased endothelial NO synthase activity including increased NO production, and reduced free radical (superoxide) formation). Endothelial derived NO has arterial vasodilatory effects which are cardioprotective (Massi et al., 2009), with 17β-estradiol linked to resting nervous tone via the autonomic nervous system. Both Huikuri et al. (1996) and Saleh & Connell (1998) independently demonstrated that 17β-estradiol is negatively associated with SNS tone and positively associated with PNS tone.
2.5 Blood Pressure Response to Exercise

A readily modifiable health behaviour that has been consistently shown to directly impact BP is exercise. The effect of exercise on human physiology can be seen in both the short-term (during an exercise bout or immediately following an exercise bout) and in the long-term (following a training program).

2.5.1 Short-term Blood Pressure Response to Exercise: During a single bout of dynamic aerobic exercise there are intensity-dependent increases in HR, stroke volume, cardiac output, and reductions of total peripheral resistance. Collectively, this results in a moderate increase in BP that increases blood flow to the working muscles (Murphy et al., 2011). Comparatively, a single bout of resistance exercise, especially isometric resistance exercise, results in substantially increased intramuscular pressure with a resulting reduction in muscle blood flow. In an attempt to overcome this intramuscular pressure barrier and maintain the perfusion pressure gradient, blood pressure spikes (Murphy et al., 2011). Traditionally, the spike in arterial BP that accompanies high-intensity isometric contractions has led some professionals to caution against resistance exercise due to concerns of adverse cardiac events (Mitchell & Wildenthal, 1974). However, a recent meta-analysis examining 28 randomized control trials with over 1012 hypertensive participants reported that during resistance training there were no adverse events reported (Cornelissen et al., 2011). Furthermore, the Canadian Hypertension Education Program now recommends that resistance training be included as a component of lifestyle modification for the control of BP even in those with HTN (Hackam et al., 2013). In specifically discussing the cardiovascular responses during isometric resistance exercise, recent literature again does not support the previously publicized concern. A systematic review of 9 randomized controlled exercise trials identified one study that assessed the response of SBP (16 ± 10mmHg), DBP (7 ± 6mmHg) and HR (3 ± 4bpm) while completing a bout of handgrip exercise (4 x 2 min @ 30% MVC) (Araujo et al., 2011). Additional research that quantifies the cardiovascular responses during-exercise will provide further evidence in support of isometric exercise safety.

Immediately following cessation of an acute bout of exercise there is a well-documented vascular phenomenon called post-exercise hypotension (PEH). PEH is characterized by a persistent drop in vascular resistance that is not offset by corresponding increases in cardiac output (Halliwill, 2001; Halliwill, Buck, Lacewell, Romero, 2013). Although, in older hypertensive patients (Hagberg, Montain, & Martin, 1987) and in endurance-trained men (Seitko, Charkoudian, & Halliwill, 2002), PEH is largely mediated by decreased cardiac output. Since it was first documented by William Fitzgerald in 1981 (Fitzgerald, 1981), PEH has been studied under various exercise conditions. By far the most widely
studied exercise modality has been aerobic exercise with PEH documented after running (Fitzgerald, 1981), swimming (Terblanche & Millen, 2012), and cycling (Endo, Shimada, Miura, & Fukuba, 2012). These acute hypotensive responses after exercise will vary depending on the intensity and duration of exercise (Eicher, Maresh, Tsongalis, Thompson, & Pescatello, 2010). However, PEH responses are similar between exercise designs when one accounts for total work, emphasizing total work as the most important factor (Jones, George, Edwards, & Atkinson, 2007). PEH following resistance training occurs less consistently and is highly variable (Macdonald, 2002).

2.5.2 Long-term Blood Pressure Response to Exercise: Numerous studies have consistently demonstrated that regular exercise training is associated with decreases in CVD risk factors in both primary and secondary prevention settings (Perez-Terzic, 2012). Exercise is recommended in several clinical guidelines (Hypertension Canada, American Heart Association) to reduce resting BP, substantiated by recent meta-analytic reviews of data (Table 2.2) indicating the efficacy of exercise modalities follow ≥ 4 weeks of training (Cornelissen & Smart, 2013).

<table>
<thead>
<tr>
<th>Exercise Classification</th>
<th>Avg $\Delta$ SBP (Mean [95% C.I])</th>
<th>Avg $\Delta$ DBP (Mean [95% C.I])</th>
<th>Additional Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endurance</td>
<td>-3.5 mmHg [-4.6 to -2.3]</td>
<td>-2.5 mmHg [-3.2 to -1.7]</td>
<td></td>
</tr>
<tr>
<td>Dynamic Resistance</td>
<td>-1.8 mmHg [-3.7 to -0.01]</td>
<td>-3.2 mmHg [-4.5 to -2.0]</td>
<td>Largest reduction for pre-HTN (-4.0 [-7.4 to -0.5] / -3.8 [-5.7 to -1.9] mmHg)</td>
</tr>
<tr>
<td>Isometric Resistance$^1$</td>
<td>-10.9mmHg [-14.5 to -7.4]</td>
<td>-6.2mmHg [-10.3 to -2.0]</td>
<td></td>
</tr>
<tr>
<td>Previous$^2$</td>
<td>-13.4mmHg [-2.6 to -2.0]</td>
<td>-7.8mmHg [-3.4 to -1.8]</td>
<td></td>
</tr>
<tr>
<td>Updated$^3$</td>
<td>-6.8mmHg [-7.9 to -5.6]</td>
<td>-3.9mmHg [-4.8 to -3.1]</td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>-1.4 mmHg [-4.2 to 1.5]</td>
<td>-2.2 mmHg [-3.9 to -0.48]</td>
<td></td>
</tr>
</tbody>
</table>

Table 2.2 Summary of Blood Pressure Changes Following Long-term Exercise Programs (Cornelissen & Smart, 2013). $^1$Isometric resistance training includes both upper and lower limb exercise designs. $^2$(Kelley & Kelley, 2010). $^3$(Carlson, Dieberg, Hess, Millar, & Smart, 2014).

These large meta-analyses are not only useful for identifying the overall effect of exercise training on resting BP, they also highlight the large amount of inter-individual variability represented by the wide confidence intervals. Statistically, this variability can lead to type II errors, as real clinical pre- to post-interventional differences may exist but with a lack of statistical power to significantly detect them. A suggestion to combat this is to (1) increase sample size numbers and/or (2) employ methods of repeated measures. Experimentally uncovering the source of inter-individual variability is one of the current research goals.

2.5.3 Considerations of Exercise Adherence: The health benefits associated with alternative lifestyle interventions, such as exercise programs, can be especially impactful for the aging population (Chodzko-
Unfortunately, despite compelling scientific research and widespread public health recommendations, only 18% of 45–64 year old women and only 11% of 65–74 year old women, perform physical activities that enhance and maintain muscle strength and endurance two or more times per week (Kruger Carlson, & Buchner, 2007). Among those who decide to adopt an exercise program, the aging population frequently displays very low level of adherence (van Heuvelen, Hochstenbach, Brouwer, de Greef, & Scherder, 2006), with approximately 50% of people who begin an exercise program discontinuing that program within six months (Hong, Hughes, Prohaska, 2008; Medina-Mirapeix, Escolar-Reina, Gascon-Canovas, Montilla-Herrador, & Collins, 2009; Kallings, Leijon, Kowalski, Hellenius, & Stahle, 2009). This can be problematic when exercise is being used for therapeutic use, given that an adherence of at least 80-85% is recommended if the results of an intervention are to be satisfactory (Pisters et al., 2010). In the aging population specifically, adherence diminishes over time (Pisters et al., 2010) with lower exercise compliance for aerobic training regimens as compared to resistance training regimens (Hong et al., 2008; Picorelli et al. 2014). With these aforementioned exercise adherence challenges in mind, ideal exercise options for this population should be both efficacious (able to produce the desired clinical outcomes under tightly controlled research restrictions) and effective (able to replicate desired outcomes under “real world” settings without research restrictions), and include considerations of exercise program adherence.

An emerging alternative exercise modality for blood pressure reduction is isometric handgrip exercise (HG). This modality can be readily accessible, has a low time commitment, and results have shown favourable modifications to resting BP (Carlson, Dieberg, Hess, Millar, & Smart, 2014; Cornelissen & Smart, 2013; Inder et al., 2015, Kelley & Kelley, 2010; Lawrence, Cooley, Huet, Arthur, & Howden, 2015; Millar, McGowan, Cornelissen, Araujo, & Swaine, 2014). Additionally, there are promising indictors of exercise adherence pertaining to long-term HG training. Among a mixed-sex sample of older adults completing ten weeks of HG exercise (two out of three training sessions per week were at-home), there was a reported exercise adherence score of 100% (Badrov, Horton, Millar, & McGowan, 2013b). The same research group again reported 100% exercise adherence to eight weeks of HG exercise (three out of five training sessions per week were at-home) (Badrov et al., 2013a). Finally, in a sample of younger men, adherence of ≥ 90% to four weeks of high intensity intermittent HG exercise was reported (Allen, Geaghan, Greenway, & Welsch, 2003).

2.6 Specific Effect of Handgrip Exercise on Blood Pressure
Handgrip (HG) exercise has emerged in the recent literature as an effective strategy for BP reduction, requiring relatively little time commitment and employing generally easy to use exercise designs. There have been documented alternations to the cardiovascular system brought on by acute HG bouts and HG training interventions.

2.6.1 Short-term Impact of a Handgrip Exercise Bout: A 2-3 minute isometric contraction task performed at 20%-40% maximal volitional contraction produces a characteristic cardiovascular response (Mitchell, 1990). Traditionally, the physiological changes associated with an isometric resistance exercise bout have been characterized as an abrupt increase in SBP, DBP and MAP, with a small rise in cardiac output due to a modest increase in HR, a stable stroke volume, and an unchanged systemic vascular resistance (calculated as MAP/cardiac output). By this original description, the rise in BP during a bout of HG exercise would be due to augmented cardiac output (Nutter, Schlant, & Hurst, 1972). Conceptual updates to our understanding of the cardiovascular response to handgrip resistance exercise reveals that alterations to intramuscular pressure can lead to increased systemic vascular resistance. As the body attempts to maintain blood flow to the working muscles there is both tachycardia and improved inotropy (Rowland & Fernhall, 2007). During an isometric handgrip contraction SNS activity to the working muscle and corresponding vasculature is augmented via both central command and the exercise pressor response (with its mechano- and metaboreflex branches) (Kaufman & Hayes, 2002), resulting in short-term impacts of HG exercise that can be discussed in terms of the response elicited during an exercise bout and following exercise cessation.

Overall, there is a lack of research characterizing the during-exercise responses to an HG bout, especially in reference to older post-menopausal women. Nonetheless, the research that exists has highly variable results regarding the short-term responses of the cardiovascular system to HG exercise. This can be partially attributed to the disparity in HG design features such as exercise intensity, grip lengths, and work-rest ratios. Regardless of the design features, the cardiovascular system reacts to a bout of HG exercise by increasing BP. This response is the result of a combination of factors (nervous, hormonal, local, etc.) with high-intensity intermittent HG exercise resulting in augmented CV drive (MAP, ≥11mmHg) (Thijssen et al., 2011) as compared to moderate-intensity continuous HG exercise (SBP, 16 ± 10mmHg; DBP, 7 ± 6mmHg; HR, 3 ± 4bpm) (Araujo et al., 2011). A comparison of two HG protocols that use the same grip intensity with differing contraction duration revealed a time-dependent effect on SBP with longer contraction times resulting in greater SBP change (Millar, MacDonald, & McCartney, 2011).
In addition to the BP responses reported during HG exercise there have also been reported post-exercise reductions in SBP immediately following ZONA exercise cessation in groups of mixed-sex (8 men; 4 women) normotensive seniors (-2 to -3mmHg) (Millar et al., 2011), and mixed-sex (9 men; 9 women) pre-hypertensive seniors (-3mmHg) (Millar, Bray, MacDonald, McCartney, 2009a). However, this post-exercise response is not universal and BP reductions were not confirmed in another study of mixed-sex (36men; 5women) seniors (Araujo et al., 2011) or older hypertensive women (Olher et al., 2013). The source of such disparity may be in the sample population, as the sex-dependent acute physiological responses to handgrip exercise are understudied among older individuals. Alternatively, the disparity may also be the result of HG protocol design features. However, older adults (70 ± 5 years, 4 women) completing isometric HG exercise at an intensity of 30% MVC with three distinct protocol designs (sets x grip duration: 4 x 2min, 8 x 1min, 16 x 30s) displayed equal post-exercise reductions in SBP and DBP as compared to a sham protocol (Millar et al., 2011). Whether work-rest ratios affect acute BP responses (instantaneous or post-exercise) among post-menopausal women is unknown.

Alternatively, physiological alterations in vascular morphology and function have been shown as a result of a HG exercise bout. During an exercise bout the increased metabolic demand causes vasodilation and increased blood flow to the working muscle tissues. As a result, shear stress \(4\eta Q/\Pi R^3\), where \(\eta=viscosity,\ Q= blood\ flow,\ \Pi=pi,\ R=\) internal radius of the artery is elevated in the vasculature that supplies these working areas (Laughlin, Newcomer, & Bender, 2008), potentially resulting in shear stress flow mediated vasodilation (Thijssen et al., 2011). Studies that have controlled the average shear experienced through a HG exercise bout have determined that post-exercise vascular response are not the result of HG exercise work-rest ratios directly, but are instead due to the average shear stimulus (King, Slattery, & Pyke, 2013). Controlling for shear stress can be accomplished in the laboratory but is nearly impossible to accomplish in a “real-world” exercise training situation. By extension, HG exercise protocols with varying design features that produce dissimilar patterns of shear stress may stimulate the local vasculature to a degree that matches average vascular shear stress. With regard to research on the resistance vessel function of post-menopausal women, the short-term impact of varying HG exercise protocols has yet to be determined.

2.6.2 Long-term Impact of Handgrip Exercise Training: In a recent review of 6 randomized controlled trials of isometric resistance exercise training reductions in resting BP were substantial (Mean, [95\%CI]) systolic ;-6.88, -8.31 to -5.46 mmHg; diastolic; -3.64, -4.69 to -2.58mmHg (Inder et al., 2015). Less restrictive inclusion criteria identified 20 prospective HG training studies of ≥ four weeks (systematic literature review currently being completed by D. Bentley, C. Nguyen, and S. Thomas (Appendix 6).
<table>
<thead>
<tr>
<th>Reference (First Author, year)</th>
<th>Research Design</th>
<th>Participants Characteristics</th>
<th>HG Protocol Design Features</th>
<th>Blood Pressure Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen, 2003</td>
<td>Cohort</td>
<td>Young (26), normotensive men (n=14)</td>
<td>5d.wk-1, for 4wks. @60%MVC</td>
<td>SBP: NS DBP: NS</td>
</tr>
<tr>
<td>Alomari, 2010</td>
<td>Cohort</td>
<td>Young (24), normotensive, men (n=11)</td>
<td>3d.wk-1, for 10wks. 60%MVC</td>
<td>SBP: NS DBP: NS</td>
</tr>
<tr>
<td>Badrov, 2013a (Badrov et al., 2013)</td>
<td>RCT</td>
<td>Young (23), normotensive, women (n=12)</td>
<td>3d.wk-1, for 8wks. 30%MVC</td>
<td>SBP: -6mmHg DBP: NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Young (27), normotensive, women (n=11)</td>
<td>5d.wk-1, for 8wks. 30%MVC</td>
<td>SBP: -6mmHg DBP: NS</td>
</tr>
<tr>
<td>Badrov, 2013b</td>
<td>RCT</td>
<td>Old (65), pre-HTN (n=12, 6women)</td>
<td>3d.wk-1, for 10wks. 30%MVC</td>
<td>SBP: -8mmHg DBP: -5mmHg</td>
</tr>
<tr>
<td>Bank, 1998</td>
<td>Cohort</td>
<td>Middle aged (40), MAP = 87.5 (n=11, 6women)</td>
<td>4d.wk-1, for 4-6wks. 30%MVC</td>
<td>MAP: NS</td>
</tr>
<tr>
<td>Dawson, 2012</td>
<td>RCT</td>
<td>Old (62), MAP = 104.2, (n=9, 1woman)</td>
<td>3d.wk-1, for 6wks. @40%MVC</td>
<td>MAP: NS</td>
</tr>
<tr>
<td>Dobrosielski, 2009</td>
<td>Cohort</td>
<td>Old (81), hypertensive men (n=12)</td>
<td>4d.wk-1, for 4wks. @70%MVC</td>
<td>SBP: -2mmHg DBP: NS</td>
</tr>
<tr>
<td>Katz, 1997</td>
<td>Cohort</td>
<td>Middle age (58), (n=12, 2women)</td>
<td>4d.wk-1, for 4wks. @max</td>
<td>MAP: NS</td>
</tr>
<tr>
<td>Kumar, 2010</td>
<td>Cohort</td>
<td>Young (23), hypertensive (n=23, 13women)</td>
<td>7d.wk-1, for 4wks. @max</td>
<td>SBP: -8mmHg DBP: NS</td>
</tr>
<tr>
<td>McGowan 2007a</td>
<td>Cohort</td>
<td>Aged (66), medicated hypertensive (n=7, 2women).</td>
<td>Unilateral: 3d.wk-1, for 8wks. @30%MVC</td>
<td>SBP: -9mmHg DBP: NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aged (62), medicated hypertensive (n=9, 2women)</td>
<td>Bilateral: 3d.wk-1, for 8wks. @30%MVC</td>
<td>SBP: -15mmHg DBP: NS</td>
</tr>
<tr>
<td>McGowan 2007b</td>
<td>RCT</td>
<td>Young (27), normotensive, (n=13, 3women)</td>
<td>4d.wk-1, for 8wks. @30%MVC</td>
<td>SBP: -5mmHg DBP: NS</td>
</tr>
<tr>
<td>Millar, 2008</td>
<td>RCT</td>
<td>Aged (66), normotensive, (n=49, 28women)</td>
<td>3d.wk-1, for 8wks. @30%MVC</td>
<td>SBP: -10mmHg DBP: -3mmHg</td>
</tr>
<tr>
<td>Millar, 2013</td>
<td>Cohort</td>
<td>Aged (66), pre-HTN (n=13, 2women)</td>
<td>3d.wk-1, for 8wks. @30%MVC</td>
<td>SBP: -5mmHg DBP: -3mmHg</td>
</tr>
<tr>
<td>Mostoufi-Moab, 1998</td>
<td>Cohort</td>
<td>Young (22), men (n=10)</td>
<td>4d.wk-1, for 4wks. 30-35%MVC.</td>
<td>MAP: NS</td>
</tr>
<tr>
<td>Piepoli, 1996</td>
<td>Cohort</td>
<td>Middle age (59), pre-HTN, men (n=18)</td>
<td>2d/3d.wk-1, for 6wks. @max</td>
<td>MAP: NS</td>
</tr>
<tr>
<td>Ray, 2000</td>
<td>RCT</td>
<td>Young (19-35), normotensive, (n=17, 8women)</td>
<td>4d.wk-1, for 5wks. @30%MVC</td>
<td>SBP: NS DBP: -5mmHg</td>
</tr>
<tr>
<td>Stiller-Moldovan, 2012</td>
<td>RCT</td>
<td>Aged (60), normotensive (n=11, 4women)</td>
<td>3d.wk-1, for 8wks. @30%MVC</td>
<td>SBP: NS DBP: NS</td>
</tr>
<tr>
<td>Taylor, 2003a</td>
<td>RCT</td>
<td>Aged (69), medicated hypertensive, (n=9, 4women)</td>
<td>3d.wk-1, for 10wks. @30%MVC</td>
<td>SBP: -19mmHg DBP: -7mmHg</td>
</tr>
<tr>
<td>Thijsen, 2011</td>
<td>Cohort</td>
<td>Young (22), pre-HTN, men (n=11)</td>
<td>4d.wk-1, for 8wks. @40%MVC</td>
<td>SBP: NS DBP: NS</td>
</tr>
<tr>
<td>Wiley, 1992</td>
<td>RCT</td>
<td>Young (20-35), normotensive, men (n=8)</td>
<td>3d.wk-1, for 8wks. @30%MVC</td>
<td>SBP: -13mmHg DBP: -9mmHg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Young-Middle age (29-52), men normotensive, (n=10)</td>
<td>3d.wk-1, for 8wks. @50%MVC</td>
<td>SBP: -10mmHg DBP: -9mmHg</td>
</tr>
</tbody>
</table>

Table 2.3. Summary of Handgrip Exercise Interventions. Significant results have been bold-typed. d, days; DBP, diastolic blood pressure; HTN, hypertension; pre-HTN, prehypertension; MAP, mean arterial pressure; min, minutes; MVC, maximal volitional contraction; NS, non-significant; RCT, randomized controlled trials; sec, seconds; SBP, systolic blood pressure; wks, weeks.
With a reduction in resting BP as the primary outcome of interest there are notable trends within the identified literature from Table 2.3. Most relevant to this work are the trends pertaining to the age of participants, the sex of participants, and the exercise intensity.

Based on the twenty identified research reports, there has yet to be a direct examination of the impact of age using HG exercise to reduce resting BP. Ten studies enrolled young participants (up to age 57, typically mid-twenties) while the remaining ten studies enrolled older participants (ages 60 years plus) with similar success in reducing resting BP; 50% success for young participants and 60% for older participants. Success in reducing resting BP can be dependent on the initial resting BP of the participants. With this in mind, perhaps the slightly heightened success of HG training among aged individuals is a result of the age-dependent rise in resting BP (Pearson, Morrell, Brant, Landis, & Fleg, 1997). A comprehensive meta-analysis is required to substantiate these apparent similarities, with enhanced precision likely able to identify the potential impact of age (possibly mediated through increased resting BP).

Among studies of older participants there are inconclusive sex-specific training findings due primarily to a lack of planned assessments. Researchers commonly recruit mixed-sex samples (Badrov et al., 2013b; Dawson et al., 2012; Katz, Yuen, Bijou, & LeJemtel, 1997; McGowan et al., 2007a; McGowan et al., 2007b; Millar et al., 2008; Millar, Bray, MacDonald, & McCartney, 2013; Millar, Levy, McGowan, McCartney, & MacDonald, 2013; Piepoli et al., 1996; Stiller-Moldovan, Kenno, McGowan, 2012; Taylor, McCartney, Kamath, & Wiley, 2003) with a few studies of men only (Dawson et al., 2012; Dobrosielski et al., 2009; Katz et al., 1997; Piepoli et al., 1996). Although no direct comparison of men and women was conducted with adequate statistical power within the same study, there are speculative conclusions that can be drawn based on research that exclusively enrolled only one sex. Research that enrolled exclusively aged men determined that four weeks of high intensity HG training reduced SBP by only 2mmHg (Dobrosielski et al., 2009) while six weeks of maximal intensity HG training resulted in no training effect on resting blood pressure (Piepoli et al. 1996). There was no published research that enrolled aged women exclusively. Alternatively, in the only study that exclusively enrolled women, albeit young women (mean age 23yrs), eight weeks of HG exercise training using 30% sustained grip contractions significantly reduced resting SBP by 6mmHg (with no change to DBP) (Badrov et al., 2013a). Future research with the primary research objective of isolating the sex-specific responses to HG exercise is required.
Finally, the design features of the exercise training program itself may directly influence the impact of a HG training intervention. The length of the exercise training study does not appear to consistently impact the success of the HG exercise intervention. Some researchers have reported significant BP reductions in as little as four weeks of very high intensity HG training (Dobrosielski et al., 2009; Kumar, Seward, Wilcox, & Torella, 2010), while others have reported insignificant changes in resting BP following eight weeks or more of high intensity HG training (Alomari, Mekary, Welsch, 2010; Katz et al., 1997) and low intensity HG training (Stiller-Moldovan et al., 2012; Thijssen et al., 2011). With a high degree of heterogeneity among the published literature with regard to training intensity, training frequency, BP measurement, and grip tool it is very challenging to make such direct comparisons. As identified by previous reviews, the most common HG training protocols use a series of sustained grip squeezes, typically 4x2min contractions, at low to moderate intensities of 20-50% maximal volitional contraction (MVC) with 1-5mins of rest in between sets, performed three to five times per week for a total of four to ten weeks (Lawrence et al., 2015; Miller et al. 2014). Although, higher intensities of 50%MVC (Wiley, Dunn, Cox, Hueppchen & Scott, 1992), 60%MVC (Allen et al., 2003) 70%MVC (Dobrosielski et al., 2009) and maximal grip intensity (Katz et al., 1997; Kumar et al., 2010; Piepoli et al., 1996) have also been employed. Future research that is designed for successive resting BP measurements for a time-dependent analysis of training outcomes is required.

2.6.2.1 Proposed Mechanisms of Long-term Training Responses: Although the exact physiological mechanisms responsible for HG training-induced reductions in resting BP remain to be elucidated, proposed mediators include favorable modifications to the autonomic control of cardiac and vascular structures (Lawrence et al., 2015; Millar et al., 2014) and improvements in peripheral vascular resistance (Carlson et al., 2014).

Training-induced alterations to peripheral vascular resistance can be determined as either the resistance of large conduit arteries (ie. usually measured by FMD) or as the resistance of the entire vascular bed including smaller arterioles (ie. measured by strain-gauge assessment of whole forearm flow). At the level of large conduit arteries, repeated exposure to elevations in shear stress, as seen with chronic exercise protocols, are the primary physiological signals for endothelial adaptations to exercise training (Padilla et al., 2011). As related to HG specifically, brachial artery endothelial improvements are abolished when localized augmentations to shear stress are experimentally prevented (Tinken et al., 2010), highlighting the importance of local perturbations to forearm flow in stimulating vascular improvements. The importance of flow-induced perturbations to local shear is further demonstrated in research comparing bilateral and unilateral exercise designs. McGowan et al. noted that in medicated hypertensive patients, 8
weeks of either unilateral (n=9) or bilateral (n=7) HG training improved endothelial-dependent FMD in the working forearms only (McGowan et al., 2007a). With respect to vascular resistance, HG exercise training increases the peak reactive hyperaemic blood flow, a marker of functional changes in vasodilatory capacity in the resistance vessels (small arteries and arterioles) (Badrov et al., 2013a; McGowan et al., 2007a). Unilateral handgrip exercise training designs reveal that improvements in forearm vascular function are restricted to the training arm only, supporting one idea of peripheral vascular adaptations (Alomari et al., 2010; Bank, Shammas, Mullen, & Chuang, 1998; Dobrosielski et al., 2009). Interestingly, exercise training has also been shown to exert systemic vascular effects in areas of the body that are inactive. Lower limb cycling has resulted in vascular improvements to both the conduit vessels (measured through FMD) and the resistance vessels (measured through forearm blood flow) of the upper limb (Padilla et al., 2011). This suggests that the volume of working muscle mass may play a role in driving local versus systemic vascular improvements, with the smaller forearm muscular volume insufficient to lead to systemic vascular improvements. Further research is required to examine this potential relationship.

With regard to training-induced alterations to resistance vessel endothelial function (estimated through strain-gauge plethysmography with reactive hyperaemia) Badrov et al. studied normotensive women who completed HG training (four, 2-min unilateral contractions at 30% MVC) either three times per week (n=12) or five times per week (n=11). The researchers found that HG training decreased systolic BP in the three times per week group (94 ± 6 to 88 ± 5 mmHg, pre- to post-training; P < 0.01) and in the five times per week group (97 ± 11 to 91 ± 9 mmHg, P < 0.01), with concomitant improvements in forearm peak reactive hyperaemic blood flow (26 ± 7 to 36 ± 9 mL/min/100mL tissue, P < 0.01; and 26 ± 7 to 38 ± 13 mL/min/100mL tissue, P < 0.01, respectively) (Badrov et al., 2013a). Improvements in peak forearm reactive flow without a change to resting flow have been confirmed among cohorts of older women completing eight weeks of whole body resistance training (22±9 to 27±10 ml/min/100mL tissue) (Rossow et al., 2014). It is unclear if a HG exercise training intervention would improve either resting forearm blood flow or peak reactive blood flow in older women. It is currently unclear if HG exercise design features, such as grip intensity or work-to-rest ratios, elicit disparate alterations to forearm blood flow in such long-term studies. As such, future research with the primary goal of assessing local resistance vessel endothelial function in response to HG training regimens would be beneficial.

In addition to the training-induced modification to peripheral vascular resistance, HG exercise has also been shown to improve autonomic control of cardiac and vascular structures (Lawrence et al., 2015; Millar et al., 2014). Autonomic nervous modulation of the vasculature manifests itself as vascular tone
and may therefore directly impact resting BP (Cornelissen et al., 2011). To determine autonomic nervous control, one can turn to the modulation of the heart, assessed using heart rate variability (HRV). HRV is representative of the oscillations in the interval between consecutive heartbeats. Assessments of HRV can provide insight into cardiac vagal and sympathetic modulation. Investigations of HRV using traditional frequency or time-domain measures may not be adequate to detect small, yet meaningful, changes in neurocardiac modulations. However, nonlinear measures of HRV have been proposed as important markers, sensitive to subtle and important modulations to HR behaviour (Makikallio et al., 2002). Using HG as an exercise training modality has successfully improved neurocardiac complexity (Sample Entropy) among older medicated hypertensive men and women (Millar et al. 2013) but not young normotensive women (Badrov et al., 2013). Assessment of sympathetically driven vasoconstriction as a result of cold-water hand submersion (aka, the Cold Pressor Test) following HG training has shown statistically insignificant changes in older (55 ±5 years) individuals, suggesting that four weeks of HG bilateral training may not be sufficient enough to elicit a response (Credeur et al., 2012).

2.6.3 The Need for an Accessible HG Exercise Option: Within the HG literature, the most common handgrip training protocols use a series of sustained grip squeezes, typically 4x2min contractions, at low to moderate intensities of 20-50% maximal volitional contraction (MVC) with 1-5mins of rest in between sets, performed three to five times per week for four to ten weeks (Lawrence et al., 2015; Millar et al., 2014). With a relatively small time commitment (<20min/session) and substantial BP reductions (Mean, [CI]) of systolic blood pressure (-6.8, -7.9 to -5.6mmHg) and diastolic blood pressure (-4.0, -4.8 to -3.1mmHg) (Carlson et al., 2014), isometric exercise has the potential to be an extremely impactful lifestyle intervention. However, exercise prescriptions that use MVC percentages as intensity values require that real-time force output during each exercise bout be regulated via supervised laboratory visits and/or specialized at-home exercise equipment. Ultimately, this limits exercise accessibility for the general population.

Accessible alternative exercise options are especially important for particular groups, such as older women, who display less than ideal adherence to traditional whole body aerobic exercise options. With age, older women are faced with various physiological declines that can be attributed to the menopause transition including a reduction in bone mineral density (Douchi et al., 2012), a loss of muscular strength and balance (Karinkanta et al., 2009), and an exponential rise in cardiovascular disease incidence (Schenck-Gustafsson, 2009). An accessible and effective exercise option, such as HG exercise, may help to improve women’s health while also introducing exercise behaviours in this at-risk population.
2.7 Summary and Conclusion

Controlling resting BP can be an impactful strategy for reducing the risk of CV disease. Even though traditional aerobic and resistance exercise options have known health benefits, unfortunately older women are still very unlikely to complete them. Alternative lifestyle modifications that are simple and easily incorporated into one’s daily routine are required. Handgrip exercise options may be one way of designing a lifestyle modification that can favourably modify resting BP while also being simple and easy to incorporate. Although HG exercise has not been demonstrated to improve other indicators of health such as total cholesterol and blood lipids (Allen et al., 2002; McGowan et al., 2007a) or weight loss (McGowan et al., 2007a; Millar et al, 2013; Stiller-Moldovan et al., 2012), the reduction in resting BP remains the primary means of decreased cardiovascular risk. The design and evaluation of novel HG exercise options should focus on both exercise efficacy and effectiveness. Exercise efficacy can be explored by isolating the acute and chronic physiological modifications of blood pressure and its correlates of vascular health and autonomic nervous health. Exercise effectiveness can be explored by considering issues of exercise behaviour and adherence.

Thus, the following studies were conducted in cohorts of older post-menopausal women to explore the acute and chronic impact of a novel, highly accessible, handgrip exercise option on various indices of cardiovascular health. Collectively, these studies were intended to examine the acute and chronic physiological impacts of maximal handgrip exercise, to broaden our understanding of the impact of handgrip exercise on the cardiovascular system by specifically focusing on aged women, and to further characterize the unique exercise-induced cardiovascular responses of post-menopausal women.
CHAPTER 3
A Direct Comparison of the Acute Cardiovascular Responses to Two Handgrip Exercise Protocols: a high intensity interval protocol and a moderate intensity sustained protocol

3.1 Introduction

Handgrip (HG) exercise training substantially reduces resting blood pressure (BP) in cohorts of older adults. Recent meta-analytic data indicates that in randomized controlled trials of at least 4 weeks, HG training substantially reduces both resting systolic BP (mean [CI])(-6.8mmHg [-7.9 to -5.6]) and diastolic BP (-3.9mmHg [-4.8 to -3.1]) (Carlson et al., 2014). Although the exact combination of physiological mechanisms responsible for this dramatic reduction in resting BP remains to be fully elucidated, several authors have proposed both favourable modifications to the autonomic control of cardiac and vascular structures (Lawrence et al., 2015; Millar et al., 2014) and improvements in vascular resistance (Carlson et al., 2014) as potential mediators. In reference to vascular resistance, HG exercise training improves peak reactive hyperaemic blood flow, a marker of functional adaptations to the resistance vessels (small arteries and arterioles) (Badrov et al., 2013a; McGowan et al., 2013a). Unilateral handgrip exercise training designs reveal that improvements to forearm vascular function are restricted to the training arm only (Alomari et al., 2010; Bank et al., 1998; Dobrosielski et al., 2009). Therefore, perturbations to local blood flow resulting from the physical impact of HG contractions may play a role in driving the improvements to forearm vascular function; a speculation that is further demonstrated by exploring the influence of HG protocol design features.

Physiological alterations to forearm blood flow are dependent on HG protocol design features, such as grip intensity and work-to-rest duty cycle. For instance, there is a threshold relationship between relative grip intensity and forearm blood flow such that measureable impedance to flow does not significantly occur until contraction intensities exceed ~20% of one’s maximal volitional contraction (MVC) (Barcroft & Millen, 1939; Barnes, 1980; Donald et al., 1967). Intermittent HG exercise completed at 30 cycles per minute elicits intensity-dependent instantaneous changes in brachial blood flow, with grip intensity of 30%MVC consistently producing greater mean and antegrade flow as compared to 5% or 15%MVC (Atkinson et al., 2015). Similar intensity-dependent alterations to forearm blood flow occur following exercise cessation, with intermittent HG exercise using graded ramp tests until task failure increasing
blood flow in proportion to forearm work load (Gonzales, Thompson, Thistlethwaite, Harper, & Scheuermann, 2007). In comparison, during sustained HG protocol designs, although both low and high intensity exercises have been shown to significantly increase forearm blood flow in both sexes, only men displayed an intensity-dependent difference in flow when comparing 20%MVC and 50%MVC sustained contractions (Thompson, Fadia, Pencivero, & Scheuermann, 2007).

Similar to forearm blood flow, the BP responses to HG exercise also depend on HG protocol design features. High-intensity intermittent HG exercise results in augmented cardiovascular drive (MAP, >11mmHg) (Thijssen et al., 2011) as compared to moderate-intensity continuous HG exercise (SBP, 16 ± 10mmHg; DBP, 7 ± 6mmHg; HR, 3 ± 4bpm) (Araujo et al., 2011). When the same exercise intensity is prescribed within two HG protocols that differ in their contraction duration only, there is a time-dependent effect on SBP with longer contraction times resulting in greater SBP change (Millar et al., 2011).

It is therefore evident that during HG exercise both forearm blood flow and BP respond according to distinct HG protocol design features, with dissimilar patterns of change to high intensity intermittent HG exercise compared with moderate intensity continuous HG exercise. Despite this potential disparity and the aforementioned importance of local blood flow in driving improvements in vascular function, few direct comparisons exist between different HG exercise designs. In fact, to our knowledge, no study has used a randomized intra-individual research design to directly compare the potentially disparate instantaneous and post-exercise acute CV responses to high intensity intermittent and moderate intensity continuous handgrip exercise designs. Given that an individual’s acute cardiovascular response (ie. change in BP or HR), either during exercise or following exercise cessation, may be related to long-term changes resulting from an exercise intervention (Liu, Goodman, Nolan, Lacombe, & Thomas, 2012), research with the primary goal of quantifying and comparing the acute CV responses to different HG exercise designs is required.

Examining the CV responsiveness to different HG exercise designs may help elucidate potentially unique reactions of specific at-risk cohorts, such as older post-menopausal women. The exponential rise in CVD in women at approximately age 55–60 years suggests that menopause augments CVD risk (Schenck-Gustafsson, 2009), with the relative-risk of developing CVD increasing fourfold after the menopause transition (Yang & Reckelhoff, 2011). Handgrip-induced BP reduction may serve as a strategy for CVD risk management in this at-risk population and requires further experimental analysis.
Therefore, in a cohort of older women, this research sought to characterize and compare the CV responses to two handgrip protocols; a common research protocol which uses 4x2min sustained grip contractions at 30% MVC intensity with 1min rests between sets (ZONA), and a novel in-house protocol of 32x5sec intermittent grip contractions at maximal intensity with 5sec rests between sets (IN-HOUSE). We characterized and compared: (1) the during-exercise cardiovascular responses of BP and HR during the exercise bouts, (2) the post-exercise cardiovascular responses of BP and HR for thirty minutes following exercise cessation, and (3) the potentially sustained influence of handgrip exercise on both resting and peak forearm blood flows.

Based on the limited available literature in this area, it was hypothesized that during the exercise bout both the continuous and the intermittent HG strategies would increase systolic BP and diastolic BP. In comparing the two strategies directly, it was hypothesized that the IN-HOUSE maximal intensity HG strategy would cause a greater during-exercise CV response given the heightened presser response expected from maximal exercise. It was also hypothesized that following the cessation of either HG intervention BP values would return to day-of resting within 30 minutes. Given that intermittent high intensity contractions would theoretically cause cyclic fluctuations to local forearm flow and promote removal of exercise metabolites, it was hypothesized that the IN-HOUSE protocol would result in a faster return of CV variables to resting values despite the augmented CV drive. Finally, it was hypothesized that both HG strategies would transiently increase resting forearm blood flow as compared to control, while peak hyperaemic flow would remain consistent across the three experimental conditions.

3.2 Methods

This study was approved by the Research Ethics Board at the University of Toronto (REB#29450) and is accordance with the guidelines set forth by the Declaration of Helsinki of the World Medical Association (2013). All participants provided written informed consent after receiving a full explanation of all experimental procedures, exercise protocols, and possible risks associated with participation in the study. All testing was performed in an isolated room (free from external noise and distractions) within the Human Health and Performance Laboratory at the University of Toronto between the hours of 2:00-8:00pm to reduce the impact of diurnal variations in blood pressure (Jones et al., 2010). To limit external perturbations to BP, prior to each experimental visit participants completed a bladder void (Fagius & Karhuvaara, 1989), a 4hr fast, a 4hr abstinence from caffeine, and a 24hr abstinence from both alcohol and strenuous activity.
Participants: Participants were recruited from the greater Toronto area using online and word-of-mouth communication strategies. Inclusion criteria were: women, post-menopausal (≥ one year since last menstrual bleed), right hand dominant, otherwise healthy. Exclusion criteria were: hypertension, regular medication use of any kind (including hormone therapy and blood pressure medications), diabetes diagnosis, current or previous cardiovascular disease, current arthritis, current smokers, otherwise unable to participate in handgrip exercise.

Research Design: The current study employed a randomized crossover design where each participant randomly completed three experimental conditions (IN-HOUSE, ZONA, and Control) on separate testing days. In total, testing was completed over five visits to the laboratory. The first visit was to screen participants for inclusion criteria and to familiarize them to the laboratory, the experimenter, the exercise protocols, and the equipment. Participants completed mock laboratory procedures where data was recorded but not analyzed. The second Baseline visit was for anthropometric measurements, collection of health and activity information using the Physical Activity Readiness Questionnaire Plus (PARQ+) (Warburton, et al., 2011)(Appendix 2a), Rapid Assessment of Physical Activity (RAPA)(Topolski et al., 2066)(Appendix 2b), an in-house questionnaire of cardiovascular risk factors (Appendix 2c), the State-Trait Anxiety Inventory (STAI)(Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1982)(Appendix 2d). During this Baseline visit measurements of radial augmentation index, carotid-radial pulse wave velocity, and forearm blood flow (resting and reactive hyperaemic) were also taken. The remaining three experimental visits, completed in random order, were designed to enable the characterization and comparison of the during-exercise and post-exercise CV responses to two HG exercise strategies against a non-exercise seated control.

Experimental Visit Design: Upon arrival, participants completed the STAI form to assess daily changes in anxiety levels and subsequently completed 15 minutes of pre-exercise seated and supported rest. The left arm was supported and fitted with an automated oscillometric brachial cuff (BpTRU Vital Signs made by BpTRU Medical Devices, model #BPM-100, BC Canada) for discontinuous BP and HR recordings during both the resting and the post-exercise recovery time points. The right arm was supported at heart level and fitted with a photoplethysmographic finger cuff (Finometer MIDI Model #2, Finapres Medical Systems, Amsterdam Netherlands) on the middle phalanx of the right third digit for beat-to-beat recordings of BP and HR during both the resting time and throughout each exercise bout. Day-of resting recordings were acquired by both devices during the final ten minutes of seated rest. Following resting assessment, BpTRU was turned off (while the brachial cuff remained physically on the participant’s arm) and Finometer collection continued. Without changing posture, participants completed one of three
interventions (IN-HOUSE, ZONA, or non-exercise seated Control). The order of interventions was randomized and participants were blind as to which they would be completing until the end of seated rest. Following the intervention, data collection with the BpTRU device resumed and participants completed 30 minutes of seated recovery. To conclude the experimental visit, participants transitioned to a supine position for forearm vascular flow assessments. A schematic of the experimental visit design can be seen in Figure 3.1.

**Interventions:** Both HG interventions were unilateral exercise with the non-dominant hand (left for all). All participants were instructed to avoid the valsalva manoeuvre and maintain regular spontaneous breathing during the exercise duration (Olher et al., 2013). This was visually monitored and confirmed by the primary investigator.

**ZONA Handgrip Exercise:** Following a pre-programmed protocol (ZonaPLUS; Zona Health, Boise, ID) participants completed four separate 2min sustained handgrip contractions at 30% MVC with 1min of rest in between repetitions. The total protocol time was 11 minutes, and the prescribed Tension-Time Product (Bystrom & Franssonhall, 1994), representative of comparative exercise effort, was 247.5 (%MVC·min).

**IN-HOUSE Handgrip Exercise:** Following the IN-HOUSE protocol participants completed thirty-two intermittent 5sec handgrip contractions at a maximal effort (attempted@100% MVC) with 5sec rests between repetitions. The comprehensive design and corresponding rationale for the IN-HOUSE HG strategy can be found in Chapter 4. The total protocol time was 5 minutes and 20 seconds, and the prescribed Tension-Time Product was 265.0 (%MVC·min).

**Non-Exercise Control:** Seated Control was time-matched to the longest exercise duration and was therefore 11 minutes of quiet, seated rest.

**Exercise Performance and Perceived Exertion:** While completing the ZONA exercise protocol participant performance was automatically calculated by the device as the percentage of time the
individual was able to successfully maintain the prescribed intensity of 30% MVC. While completing the IN-HOUSE exercise protocol performance was described in two ways; the average force output throughout the duration of exercise (expressed as a percentage of MVC) and the corresponding logarithmic decline. In addition, during each HG bout participants indicated their rating of perceived exertion (RPE) using the Borg 6-20 RPE scale (Borg, 1982) at the midway point and at the end of exercise.

**Cardiovascular Measurements:**

**Resting Cardiovascular Values:** The BpTRU oscillometric pneumatic brachial cuff recorded SBP, DBP and HR every two minutes for the final 10 minutes of seated rest. Of these 6 recordings, the highest and lowest values were dropped, and the remaining 4 values averaged. This average BpTRU value was recorded as an individuals’ day-of resting value, and consistency statistics applied to the resting data the Baseline, Control, IN-HOUSE, and ZONA visits.

**During-exercise Cardiovascular Responses:** Using continuous beat-to-beat data from the Finometer MIDI photoplethysmograph, the during-exercise cardiovascular (SBP, DBP, and HR) responses during each of the experimental conditions were calculated as the change from the respective day-of resting value. For Finometer data, day-of resting values were determined as the average of the remaining eight per-minute values after omitting the highest and lowest. During each of the experimental exercise conditions beat-to-beat raw data was converted into 5sec averages and expressed as a change score from the previously calculated day-of rest. The results of the during-exercise cardiovascular reactivity were then quantified as an average change score encompassing the entire intervention, a peak CV response representing the greatest 5 second change score, and an area-under the-curve (AUC) score relative to intervention time. Finally, rate-pressure product, a valid index of myocardial oxygen demand during static exercise (Nelson et al., 1974), was calculated using peak HR and peak SBP values.

**Post-exercise Cardiovascular Responses:** Using data from the BpTRU oscillometric pneumatic cuff the post-exercise cardiovascular (SBP, DBP, and HR) responses following each of the experimental conditions were calculated as a change from the respective day-of resting value. As previously described, for BpTRU data day-of resting was determined as the average of the remaining 4 values after omitting highest and lowest values. Following exercise cessation post-exercise values were recorded by the BpTRU once every three minutes throughout the entire 30 minutes of the post-exercise recovery for a total of 11 readings. At each three minute interval the change score was calculated as the difference from day-of resting. Results of the post-exercise recovery responses were segmented into two sections: Recovery 1 (R1) was the average of 5 readings from the first half of recovery (0:00-14:59mins) and Recovery (R2) was the average of 6 readings from the second half of (15:00-30:00mins).
**Arterial Augmentation Index and Pulse-wave Velocity**: During the baseline visit, participants rested in a supine position for 10min after being set up for arterial assessments of radial augmentation index (AIx) and carotid-radial peripheral pulse wave velocity (crPWV). Radial AIx was determined by applanation tonometry of the right radial artery using a pressure transducer and the SphygmoCor (Model-EM3, Atcor Medical, Sydney, Australia, Software Version 8.2). AIx has been proven to be both reliable (Currie et al., 2009) and reproducible (Papaioannou et al., 2004), with confirmed reproducibility of this method determined in our laboratory among a cohort of young mixed-sex individuals previously reported (ICC: 0.90, p<0.01) (Appendix 5: (Bentley & Thomas, 2014)). Participants’ AIx score was the average of two sequential readings taken on the right side. Carotid-radial PWV was determined by sequential acquisition of pressure waveforms from the carotid and the radial arteries by use of the same tonometer. The radial and carotid pulses were located by palpation with the optimal tonometer location selected as the position that yielded the best quality signal output. The timing of these waveforms was compared with that of the R wave on a simultaneously recorded ECG. Velocity was calculated as the difference in carotid to radial path length divided by the difference in R wave to waveform foot times. Path lengths were measured as a straight line from the suprasternal notch to the carotid and radial measurement sites, respectively. Participants’ PWV score was the average of two sequential readings taken on the right side.

**Resistance Vessel Endothelial Function**: Resting and hyperaemic forearm blood flow was assessed using mercury-in-Silastic strain gauge plethysmograph as previously described (Sinoway et al., 1987). There is a highly significant correlation between endothelial function evaluated by strain gauge plethysmography and brachial artery ultrasound (Irace et al., 2001). In brief, measurements of resting blood flow were followed by 5 minutes of ischemia and subsequent measurement of resulting peak flow by means of intermittent venous occlusion. All flow measurements were performed on the non-dominant exercised arm (left for all), that was raised and supported above heart level to allow spontaneous emptying of the veins. Two inflatable cuffs were placed on the upper limb; a standard sized brachial cuff was placed proximal to the olecranon fossa and a paediatric cuff was placed at the wrist joint. The strain gauge was positioned around the forearm at the point of largest circumference approximately 3cm distal to the olecranon fossa. Flow assessment began with the rapid inflation of the wrist cuff to 200mmHg to occlude hand blood flow. Resting flow was determined by intermittently inflating the brachial cuff to 50mmHg for 10sec with 5sec of deflation. This pressure effectively blocks venous outflow while allowing arterial inflow into the forearm. Four cycles were permitted to lapse and the average flow of the last three cycles was calculated as resting flow. Ischemia was then induced by inflating the brachial cuff to 200mmHg for 5 minutes, after which the brachial cuff was rapidly deflated and intermittent cycles of venous occlusion were completed. Each flow value was calculated using an in-house software analysis program that
calculates the slope of a line drawn using the first three beats (omitting cuff inflation artefact). All flow values are expressed as mL\textperiodcentered min\textsuperscript{-1}•100mL\textsuperscript{-1}.

**Statistical Analysis:** This research was powered to assess the primary research objective of comparing the instantaneous and post-exercise response of SBP between two handgrip protocols. Based on heterogeneous literature of older adults completing HG, BP responds to the ZONA protocol with published SBP changes of 16±10mmHg (Araujo et al., 2011) and rest to exercise of 122±11 to 129±11 (Millar et al., 2011). It was determined that a difference in instantaneous SBP reactivity of at least 7mmHg between exercise conditions would be meaningful. With an alpha of 0.05 and a beta of 0.20, the required sample size for an intra-individual comparison was sixteen. Reliability statistics were determined using intraclass coefficients of variation with Cronbach’s alpha reported. Instantaneous cardiovascular responses to each experimental intervention were analyzed using Finometer change scores and one-way repeated measures ANOVA with Bonferroni post-hoc comparisons. The post-exercise cardiovascular recoveries were analyzed using BpTRU change scores and a two-way analyses of variance (ANOVA) with repeated measures to assess changes over time (R1 and R2) and between IHG protocols (IN-HOUSE and ZONA), as compared to Control. One-way repeated measures ANOVA with Bonferroni post-hoc comparisons were used to assess differences in resting blood flow between visits, differences in peak blood flow between visits, and baseline differences in BP and HR measures. Paired t-tests were used to compare tension-time products and ratings of perceived exertions. Pearson correlation coefficients were used to assess possible relationships between assessed measures. Statistical analyses were completed using IBM SPSS Statistics 23 (SPSS, Chicago, IL). All data reported as MEAN ± SD, unless specified otherwise. Significance was set at a P value of 0.05.

### 3.3 Results

**Participants:** In total, 23 women reported to the laboratory for an initial familiarization session. Upon evaluation of criteria, three women were excluded because they were left-handed (n=1), unable to commit to the timing of sessions (n=1) and had self-reported fibromuscular dysplasia in the left carotid artery (n=1). After confirmation of inclusion criteria, 20 healthy older (Mean ± SD, range)(57.7 ± 5.2yrs, 50 to 67) women participated and completed this study. On average, participants were moderately active (RAPA: 7.4 ± 2.1, 5.0 to 10.0), overweight (BMI: 26.9 ± 3.7kg/m\textsuperscript{2}, 19.0 to 33.4), normotensive (SBP: 109.1 ± 9.1mmHg; DBP: 73.3 ± 7.7mmHg; HR: 71.5 ± 7.0bpm), and at least 1 full year post-menopausal (8.4 ± 5.6, 1.0 to 22.0) (Table 3.1). All participants self-reported to be non-smoking, without any current medical conditions, and not currently taking any prescription medication. Twelve women had a self-
reported family history of heart disease, but all other non-modifiable (sex, age, ethnicity) and modifiable (smoking status, cholesterol level, BP, diet, daily stress, alcohol consumption, activity level, weight, diabetes mellitus diagnosis) risk factors remained low.

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<th>Mean ± SD (range)</th>
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<tr>
<td>Resting Systolic Blood Pressure (mmHg)</td>
<td>109.1 ± 9.1 (95.3 to 135.8)</td>
</tr>
<tr>
<td>Resting Diastolic Blood Pressure (mmHg)</td>
<td>73.3 ± 7.7 (60.7 to 91.9)</td>
</tr>
<tr>
<td>Resting Heart Rate (bpm)</td>
<td>71.5 ± 7.0 (60.6 to 88.6)</td>
</tr>
<tr>
<td>Augmentation Index</td>
<td>31.0 ± 7.6 (17.0 to 43.5)</td>
</tr>
<tr>
<td>Pulse Wave Velocity (m/s²)</td>
<td>7.2 ± 0.5 (6.3 to 8.3)</td>
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<tr>
<td>Grip Strength (non-dominant) (kg)</td>
<td>19.2 ± 4.5 (9.8 to 25.3)</td>
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<tr>
<td>Grip Strength (dominant) (kg)</td>
<td>21.7 ± 4.7 (13.8 to 30.3)</td>
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Table 3.1 Descriptive Cardiovascular Measurements. bpm, beats per minute; kg, kilogram; mmHg, millimetre of mercury; SD, standard deviation.

**Exercise Performance and Perceived Exertion:** All participants successfully completed each of the handgrip exercise protocols. Compliance to ZONA was high with all participants earning a score of >91% (96.3 ± 2.3%, 91 to 100). In comparison, although the IN-HOUSE HG protocol was prescribed as maximal intensity, the average relative performance throughout was moderate-high (50.4 ± 12.8%, 39 to 90) with a logarithmic decline of \( y = -6.45\ln(\text{time (min)}) + 80.9 \). As such, there was a resulting discrepancy in the Tension-Time Product (TTP) between the two protocols (IN-HOUSE: 134.2 ± 33.9; ZONA: 238.4 ± 5.6, p<0.001). Despite the reduced TTP, participants expressed greater ratings of perceived exertion while completing the IN-HOUSE protocol (13.2 ± 2.7) than while completing ZONA (12.1 ± 2.4, p<0.05).

**Cardiovascular Measures:**

**Resting Cardiovascular Values:** All descriptive statistics have been presented in Table 3.1. Intra-individual day-of resting values for BP and HR were not statistically different between visits (p > 0.05) and intra-class correlation coefficients of consistency, as described using Cronbach’s Alpha, were consistently high (SBP: 0.93; DBP: 0.94; HR: 0.92) among the 4 study visits. As such, the instantaneous and post-exercise BP and HR responses have been presented in reference to Control values. Furthermore, STAI scores were consistent between visits for both state (\( \alpha = 0.88 \)) and trait (\( \alpha = 0.97 \)) anxiety with no impact of STAI scores on day-of BP or HR values (p>0.05). Baseline arterial augmentation index was 29.3 ± 9.1 (\( \alpha = 0.9, p<0.01 \)) and crPWV was 7.2 ± 0.5 m/s² (\( \alpha = 0.6, p<0.05 \)).

**During-Exercise Cardiovascular Responses:** While completing high intensity intermittent HG exercise, participants experienced augmented average instantaneous systolic BP responses (IN-HOUSE: 24.1 ± 12.1 mmHg, ZONA: 15.1 ± 7.6 mmHg, p<0.01) and diastolic BP responses (IN-HOUSE: 10.9 ± 6.7, ZONA: 6.6 ± 3.6, p<0.05). This augmented cardiovascular response to IN-HOUSE handgrip exercise was
confirmed when comparing peak BP changes and relative AUC values (Table 3.2), revealing a robust
difference despite a shorter overall exercise duration (IN-HOUSE: 5mins20sec; ZONA: 11mins) and a
reduced Tension-Time Product (IN-HOUSE: 134.2 ± 33.9; ZONA: 238.4 ± 5.6, p<0.001). Although HR
was significantly elevated during both HG protocols, represented by both average (IN-HOUSE: 4.8 ± 4.5;
ZONA: 2.8 ± 3.5, p<0.05) and peak (IN-HOUSE: 13.8 ± 7.1; ZONA: 12.5 ± 6.3, p<0.05) values, there
was no difference in the HR response between the two protocols. The rate-pressure product resulting from
each HG exercise design was low and insignificantly different from each other (IN-HOUSE: 12811.6 ±
2362.9, ZONA: 12876.1 ± 3094.8, p>0.05).

<table>
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<tr>
<th>(Mean ± SEM)</th>
<th>Peak Response (5sec average)</th>
<th>Relative AUC (mmHg)</th>
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<tbody>
<tr>
<td></td>
<td>ZONA</td>
<td>IN-HOUSE</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>35.7 ± 2.5</td>
<td>42.2 ± 3.2*</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>15.9 ± 1.0</td>
<td>21.2 ± 1.8**</td>
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<td>HR (bpm)</td>
<td>12.5 ± 1.4</td>
<td>13.8 ± 1.6</td>
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Table 3.2 During-Exercise Cardiovascular Responses to Handgrip Exercise. Calculated as (1) Peak Response =
greatest 5sec deviation and (2) AUC relative to the corresponding exercise duration. Statistically different from
Zona: *p < 0.05, **p < 0.01. AUC, area under the curve; bpm, beats per minute; mmHg, millimeter of mercury; sec,
seconds; SEM, standard error of the mean;

Figure 3.2 During-Exercise Cardiovascular Responses to Two Handgrip Exercise Strategies. Results are presented
as (MEAN±SEM) change scores from rest, after comparing to control condition. *p<0.05, **p<0.01.
Post-Exercise Cardiovascular Response to HG Exercise: Despite the augmented instantaneous BP during the IN-HOUSE exercise protocol, both SBP and DBP rapidly returned to day-of resting values relative to control within the first recovery window (less than 15 min) following exercise cessation (SBP: 0.0 ± 7.4mmHg; DBP: 0.0 ± 4.7mmHg). In comparing the SBP recovery response over time (R1, R2) and between protocols (ZONA vs. IN-HOUSE), there was a significant main effect of protocol with ZONA handgrip exercise producing sustained SBP increases over the entire thirty minute post-exercise duration (+3.6 ± 8.1mmHg) as compared to IN-HOUSE (-0.1 ± 6.4mmHg) (F(1,19)=6.8, p < 0.05). This trend is replicated when comparing the DBP response over time, with ZONA producing heightened DBP (2.0 ± 4.9mmHg) over the entire thirty minutes as compared to IN-HOUSE (-0.4 ± 4.3mmHg) (F(1,19)=4.45, p <0.05). There was an insignificant interaction effect of time and strategy for the BP responses (Figure 3). Following IN-HOUSE exercise there was an insignificant trend of HR to decrease relative to control over the R1 (-0.9 ± 12.7bpm) and R2 (-1.0 ± 11.6bpm) recovery windows (p > 0.05). In comparison, following ZONA there was an insignificant trend of HR to increase over R1 (+1.2 ± 12.0bpm) and R2 (1.3 ± 11.2bpm) recovery windows (p > 0.05).

Figure 3.3 Post-Exercise Cardiovascular Responses to Two Handgrip Exercise Strategies. Results are presented as (MEAN±SEM) change scores from rest for the two handgrip interventions, after comparing to control condition. R1, recovery time-point 1 (0:00-14:59); R1, recovery time-point 2 (15:00-30:00). *p<0.05.
Resistance Vessel Endothelial Function: One-way repeated measures ANOVA revealed that neither resting forearm blood flows ($p = 0.40$) nor peak reactive hyperemic blood flows ($p = 0.96$) were significantly different between experimental conditions (Table 3.3).

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Control</th>
<th>IN-HOUSE</th>
<th>ZONA</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Mean ± SEM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting mean blood flow (ml/min/100ml tissue)</td>
<td>2.7 ± 0.3</td>
<td>2.4 ± 0.2</td>
<td>2.56 ± 1.1</td>
<td>2.7 ± 0.3</td>
</tr>
<tr>
<td>Peak 1 (ml/min/100ml tissue)</td>
<td>37.7 ± 3.4</td>
<td>40.0 ± 3.0</td>
<td>41.8 ± 2.2</td>
<td>43.8 ± 3.2</td>
</tr>
<tr>
<td>Peak 2 (ml/min/100ml tissue)</td>
<td>18.6 ± 1.8</td>
<td>16.8 ± 1.5</td>
<td>18.6 ± 8.4</td>
<td>18.0 ± 1.8</td>
</tr>
<tr>
<td>Peak 3 (ml/min/100ml tissue)</td>
<td>12.6 ± 1.5</td>
<td>10.7 ± 1.1</td>
<td>11.4 ± 1.5</td>
<td>12.1 ± 1.7</td>
</tr>
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Table 3.3 Resting and Peak Forearm Blood Flow. During the three experimental visits (Control, IN-HOUSE and ZONA) flow values were acquired approximately 45 minutes following intervention. Flow responses between visits were not significantly different from each other.

3.4 Discussion

The present study was designed to characterize and directly compare the CV responses to two HG protocols with contrasting HG design features; a high intensity intermittent (IN-HOUSE) protocol and a moderate intensity sustained (ZONA) protocol. In comparison to ZONA, although the IN-HOUSE intervention took less time to complete (IN-HOUSE: 5min20sec vs ZONA: 11min) and required less exercise effort as calculated through the Tension Time Product (IN-HOUSE, 134.2 ± 33.9; ZONA, 238.4 ± 5.6, $p<0.001$), participants perceived greater exertion (IN-HOUSE: 13.2 ± 2.9, ZONA: 12.1 ± 2.4, $p<0.05$). There were also distinct instantaneous and post-exercise cardiovascular responses to the two protocols. During the exercise bout, the IN-HOUSE handgrip protocol provoked a stronger BP response than the ZONA protocol with equivalent HR responses. Following exercise cessation, the BP response provoked by the IN-HOUSE protocol recovered to day-resting values swiftly while the BP response provoked by the ZONA protocol remained significantly elevated throughout the entire thirty minutes of recovery. Despite the dissimilar BP responses to intermittent and sustained HG exercise protocols, neither intervention produced sustained alterations to either resting forearm blood flow or peak reactive forearm blood flow. The results of the present research can be interpreted by considering autonomic nervous control of BP and HR during exercise.

*Instantaneous and Post-Exercise CV Responses:* During an acute exercise bout, the mechanisms underlying the instantaneous BP and HR responses include both “central command” and the “exercise pressor reflex; EPR” (comprised of the muscle mechanoreflex and the metaboreflex). Central command is a feedforward neural mechanism originating from the volitional intent to exercise which increases BP by withdrawal of parasympathetic nerve activity and increases in sympathetic nerve activity (Ciriello, Caverson, & Polosa, 1986; Goodwin, McCloskey, & Mitchell, 1972; Krogh & Lindhard, 1913). It has
previously been demonstrated that the influence of central command is independent of exercise intensity and is alternatively correlated to an individual’s perceived exertion (Williamson et al., 2006). In contrast, the EPR is a feedback peripheral neural reflex that originates in contracting skeletal muscle during exercise, with two groups of fibers that independently participate in the muscle mechanoreflex (group III, thinly myelinated fibers) and the muscle metaboreflex (group IV, unmyelinated fibers) (Kaufman & Hayes, 2002). The mechanoreflex is rapidly stimulated by mechanical distortion of intramuscular receptors, proportional to the peak tension developed by the working muscle (Hayward, Wesselmann, & Rymer, 1991; Kaufman, Longhurst, Rybicki, Wallach, & Mitchell, 1983; Mense & Stahnke, 1983). During static or isometric contractions, the discharge rate of the mechanoreceptor decreases as the working muscle fatigues (Hayward et al., 1991; Kaufman et al., 1983; Kaufman & Hayes, 2002). The metaboreflex is stimulated by the chemical milieu produced by exercising muscle with notable metabolites such as [H+], [bradykinin], [K+], [lactic acid], and adenosine (Kaufman & Hayes, 2002; Murphy et al., 2011). Metabolite accumulation is amplified with prolonged static contractions at intensities that limit local blood flow to the working skeletal muscle, as seen in isometric contractions of >20% MVC (Barcroft & Millen, 1983; Barnes, 1980; Donald et al., 1967).

Although, the current research was not designed to isolate the individual influence of each neural pathway on the instantaneous CV response to exercise, simple correlations to explore relationships between variables may help inform future research. For example, the influence of central command can be estimated by examining the relationship between an individual’s rating of perceived exercise exertion and their corresponding CV responses, whereas the influence of the mechanoreflex can be estimated by examining the correlation between an individual’s handgrip intensity and their corresponding CV responses. In regards to central command, the current research results show no relationship between average RPE scores and average instantaneous SBP (IN-HOUSE: r=−0.08, ZONA: r=0.22), DBP (IN-HOUSE: r=−0.06, ZONA: r=0.35), or HR (IN-HOUSE: r=0.05, ZONA: r=0.07) responses during either handgrip strategy (p>0.05 for all). This indicates that during HG exercise the instantaneous CV response may not be driven by central command, regardless of exercise design. On the other hand, there is a strong relationship between an individual’s IN-HOUSE grip intensity and their corresponding average instantaneous changes in SBP (r=0.53, p<0.05), DBP (r=0.55, p<0.05), and HR (r=0.65, p<0.01). This suggests CV responses during IN-HOUSE handgrip exercise may be driven by the mechanoreflex. The relationship between HG intensity and average CV responses are not replicated during the ZONA exercise. Although local metabolite concentrations were not directly measured, these findings suggest that the CV responses during ZONA handgrip exercise may be driven predominantly by the metaboreflex, a speculation that can be further explored when considering the sustained post-exercise responses.
The ZONA handgrip strategy calls for 2 minutes of sustained forearm contractions at 30% MVC, an intensity great enough to limit forearm blood flow for the duration of the sustained contraction (Barcroft & Millen, 1983; Barnes, 1980; Donald et al., 1967). A mismatch between blood flow and metabolism in the exercising muscle causes a change in the concentration of metabolites that is detected by metabolite-sensitive nerve endings with the skeletal muscle interstitium (Mostoufi-Moab, Widmaier, Cornett, Gray, & Sinowat, 1998). In combination, the enhanced metabolite accumulation and limited metabolite removal increases sympathetic nerve activity (Victor, Bertocci, Pryor, & Nunnally, 1998) resulting in vasoconstriction-mediated rises in BP (Seals 1989; Sinoway et al., 1989). Recently, it has been demonstrated that post-menopausal women have an exaggerated BP response to exercise that is mediated, in part, by an overactive metaboreflex with enhanced peripheral vasoconstriction (Choi et al., 2012). If the ZONA handgrip strategy is indeed causing an enhanced metaboreflex reaction, perhaps the resulting vasoconstriction is causing sustained BP responses that extend into the post-exercise recovery period. Future research designed to determine both the magnitude of reactivity response to metabolite accumulation and the associated duration of the prolonged reactivity would be instrumental in further elucidating this relationship.

The instantaneous cardiovascular reactivity and the sustained post-exercise cardiovascular responses to HG exercise in this cohort of older women suggest that the autonomic influences of the exercise pressor reflex may be independently reacting to distinct design features of the IN-HOUSE and ZONA handgrip exercise strategies. Specifically, although neither the metaboreflex nor the mechanoreflex were directly measured, the results of the present study suggest that in a cohort of post-menopausal normotensive women the mechanoreflex may be predominantly activated during high-intensity intermittent HG exercise while the metaboreflex may be predominantly activated during sustained moderate intensity HG exercise. Given the enhanced metaboreflex response present among post-menopausal women, women may display different training responses to handgrip exercise programs which combine various exercise design features. Future research with the primary goal of describing and characterizing the autonomic nervous response to both handgrip protocols will lend support to these speculations.

In addition to our primary research objective, we were also interested in determining if HG exercise could produce post-exercise hypotension among this specific cohort of normotensive women as previous research has been inconsistent. Significant post-exercise reductions in SBP have been previously reported immediately following ZONA exercise cessation in groups of mixed-sex (8 men; 4 women) normotensive seniors (-2 to -3 mmHg) (Millar et al., 2011), and mixed-sex (9 men; 9 women) pre-hypertensive seniors (-3mmHg) (Millar et al., 2009a). However, post-exercise BP reductions were not confirmed in groups of
mixed-sex (36 men; 5 women) seniors (Araujo et al., 2011) or older hypertensive women (Olher et al., 2013). The source of such disparity may be in the sample population, as the sex-dependent acute physiological responses to handgrip exercise are understudied among older individuals. A strength of the current research was the directed and targeted sample population. Here, we show that HG exercise following the traditional prescription pattern of 4 x 2 min at 30% MVC results in a sustained elevations of blood pressure over thirty minutes of recovery, as compared to a control session. In comparison, despite augmented instantaneous cardiovascular responses to a modified, high intensity handgrip protocol, cardiovascular variables return to resting values within the first fifteen minutes of exercise recovery. However, neither HG exercise protocol used in this study caused post-exercise hypotension among post-menopausal women, perhaps due to their low-normal resting BP.

**Resistance Vessel Endothelial Function:** The current results do not support a sustained impact of handgrip exercise on forearm blood flow for either resting or peak responses. The reported resting flow values of this research are consistent with other research groups who have studied similar cohorts of aged individuals and reported resting flow values of 3.2 ml/min/100 ml among aged women (Rossow et al., 2014), 3.1 ml/min/100 ml among an aged mixed-sex sample (Bank et al., 1998), and 2.0 ml/min/100 ml in young women (Gonzalves et al., 2007). Although this research shows that local brachial occlusion produces significant reactive hyperemic flows, there was no significant difference in peak flow resulting from the dissimilar handgrip protocols. Our results are in contrast with studies which have previously determined an intensity-dependent response of hyperemic peak flow, with acute HG exercise at 30% MVC causing peak FBF of 8.8 ± 1.8 and HG exercise at 45% MVC causing peak FBF of 19.6 ± 3.7 (Bank et al., 1998). The reason for the difference in results is not entirely clear. One potential explanation is the timing of the blood flow assessments. We completed our blood flow assessments following the post-exercise recovery time of 30 minutes and allowed for a transition from sitting to supine. However, others have reported improvements in forearm vascular function following HG exercise can be detected for up to 60 minutes (5.9 ± 2.8 to 10.4 ± 5.8 %, p = 0.01) (Atkinson et al., 2015). An interesting, yet speculative, explanation is the impact of menopause. Atkinson et al. studied younger (27 ± 3 yrs) men and Bank et al. studied middle-aged men and pre-menopausal women (40 ± 4 yrs). Our participants were post-menopausal for at least 1 year, without hormone replacement therapy. Circulating estrogens are known to directly impact vascular assessments (Hashimoto et al., 1995; Lieberman et al., 1994) with estrogen loss resulting in impaired FMD (an endothelium-dependent responses predominantly mediated via enhanced endothelial NO synthesis), and reduced resting and peak blood flows (O’Donnell et al., 2011). Therefore, it appears as though the intensity-dependent vascular alterations present in other cohorts are either not apparent among post-menopausal women or are quick to dissipate. Since the current research was not
designed to assess the impact of estrogens on forearm vasculature, future research with this as a primary research goal is needed to elucidate some of these potential reasons for the unique vascular responses of aged women.

**Limitations and Future Directions:** In the past, isometric exercise has been discouraged by health professionals for fear of leading to a cardiovascular event. Results of the peak instantaneous reactivity to HG exercise indicate that this concern is not warranted in the cohort of normotensive, otherwise healthy, post-menopausal women. As identified via five second peak responses, neither ZONA (SBP: 145.0 ± 20.3mmHg; DBP: 89.6 ± 9.3mmHg) nor IN-HOUSE (SBP: 150.3 ± 20.1mmHg; DBP: 89.6 ± 9.5mmHg) exercise protocols resulted in absolute BP levels of concern (SBP:>250mmHg and/or DBP:>115mmHg) (American College of Sports Medicine, 2013). Although this research supports the use of HG exercise among otherwise healthy normotensive post-menopausal women, the homogenous sample limits the application of these results. Future studies should seek to confirm the instantaneous and post-exercise cardiovascular responses among those with above ideal resting blood pressures. Finally, the conclusions in regard to the influence of the autonomic nervous system are speculative. Future research with the primary research goal of mechanistically determining these CV drivers is required to confirm these speculations.
CHAPTER 4

The Design and Evaluation of Both an Exercise Protocol and a Handgrip Tool for use as the Maximal INTerval (MINT) Handgrip Training Strategy

4.1 Introduction

Recently, there has been a strong expression of desire by both clinicians and patients for research dedicated toward alternative treatment options, such as lifestyle interventions, for the management and improvement of one’s health (Crowe, Fenon, Hall, Cowan, & Chalmer, 2015). One of the ways that lifestyle interventions, such as physical activity and exercise, can result in positive health outcomes is through the management of one’s resting blood pressure (BP) (Chodzko-Zajko et al., 2009). For example, isometric exercise, specifically isometric handgrip (HG) exercise, has been prescribed as a lifestyle intervention to successfully reduce resting BP among heterogeneous groups of participants (Carlson et al., 2014; Lawrence et al., 2015; Millar et al., 2014). Within this literature, the most common HG training protocols use a series of sustained grip squeezes, typically 4x2min contractions, at low to moderate intensities of 20-50% maximal volitional contraction (MVC) with 1-5mins of rest in between sets, performed three to five times per week for a total of four to ten weeks (Lawrence et al., 2015; Millar et al., 2014). With a relatively small time commitment (<20min/session) and substantial BP reductions (Mean, [CI]) of systolic BP (-6.8, -7.9 to -5.6mmHg) and diastolic BP (-4.0, -4.8 to -3.1mmHg) (Carlson et al., 2014), isometric exercise has the potential to be an impactful lifestyle intervention. However, HG exercise prescriptions that use MVC percentages as the prescribed intensity require that force output during exercise bouts be regulated via supervised laboratory visits and/or expensive specialized at-home exercise equipment. Ultimately, this limits exercise accessibility for the general population.

Accessible alternative exercise options are especially important for particular groups, such as older women. Despite compelling scientific research and widespread public health recommendations, among women 45–64 years and 65–74 years old, only 18% and 11%, respectively, perform physical activities that enhance and maintain muscle strength and endurance two or more times per week (Kruger et al., 2007). With age, older women are faced with various physiological declines that can be attributed to the menopause transition including a reduction in bone mineral density (Douchi et al., 2002), a loss of muscular strength and balance (Karinkanta et al., 2009), and an exponential rise in cardiovascular disease incidence (Schenck-Gustafsson, 2009). An accessible and effective exercise option, such as isometric
handgrip exercise, may help to improve women’s health through blood pressure reduction while also introducing positive exercise behaviours in this at-risk population.

In order to enhance the accessibility of HG exercise while maintaining intensity at a prescribed MVC percentage, adjustments can be made directly to the grip tool. For example, researchers have preserved control over moderate-intensity force output using less sophisticated grip tools with resistance-specific rubber bands (Bank et al., 1998) and springs (Millar et al., 2008; Mostoufi-Moab et al., 1998; Sinoway et al., 1996) that can be adjusted to the desired tension. However, a major limitation to both of these approaches is that regular laboratory visits are required to monitor changes in grip strength and consequently adjust the spring and/or band tension throughout the training program. To eliminate the necessity for either specialized equipment or frequent laboratory follow-ups, HG exercise protocols can prescribe maximal grip force against generic grip objects.

Protocols using maximal grip force against generic grip objects have successfully induced positive cardiovascular adaptations such as collateral vascular recruitment and growth (Lin, Chen, Li, Li, & Lu, 2014), reduced BP and improved local blood flow (Kumar et al, 2010), and reduced ergoreflex activity resulting in an improved CV response to exercise (Piepoli et al., 1996). Despite these noted positive impacts on cardiovascular indices of health, the widespread use of this highly accessible exercise option has yet to be fully integrated by health care providers and exercise professionals. Apprehension towards integration may be due to the lack of experimental evidence regarding the acute physiological responses to maximal grip exercise and the associated determination of exercise safety; a necessity if such a design would be promoted for at-home training. Furthermore, the literature lacks a substantive assessment of participant perceptions and opinions regarding high intensity HG exercise, information that would be most useful for anticipating exercise uptake and adherence. This information would be especially useful as a direct comparison to the more conventionally used handgrip protocols, such as the ZONA protocol that uses 4x2min sustained grip contractions at 30% MVC with 1min of rest in between sets.

4.2 General Research Design

This research describes the comprehensive design and evaluation of the Maximal INTerval (MINT) handgrip exercise strategy, consisting of both a novel exercise protocol and an original grip tool. Part 1 of this research is dedicated to the MINT exercise protocol, beginning with the theoretically driven conceptualization of a highly accessible exercise option for at-home exercise training that considers the unique physiological responses of older women to HG exercise. The subsequent experimental assessment
of the MINT exercise protocol was conducted to: (1) quantify participant’s handgrip performance while following the maximal intensity exercise prescription: (2) describe the acute cardiovascular responses to MINT in reference to published exercise safety recommendations: and (3) collect participant feedback regarding the MINT protocol. Part 2 of this research describes a product development opportunity that arose as a result of participant feedback from Part 1 which identified a need for a handgrip tool that would be better suited for maximal grip contractions. The creation of the MINT grip tool began with a mixed-methods assessment of participant opinions regarding two distinct in-laboratory grip tools. These qualitative and quantitative opinions informed the creation of four unique mock-MINT tools that were critiqued and compared against not only each other but also against the original two in-laboratory tools using structured focus groups. The participant-preferred design features were combined, resulting in the final MINT handgrip tool. The MINT handgrip strategy was designed and tested specifically for use among older post-menopausal women, a cohort at increased cardiovascular risk as a result of the physiological changes associated with the menopause transition.

All components of the presented research were approved by the Research Ethics Board at the University of Toronto (REB#29450, REB#31450). Experimental assessments are in accordance with the guidelines set forth by the World Medical Association in the Declaration of Helsinki (2013). At each stage of this research, participants received a full explanation of all experimental procedures, exercise protocols, and possible risks associated with participation in the study prior to providing written informed consent. All testing was performed in the Human Health and Performance Laboratory at the University of Toronto. Physiological experiments were conducted between the hours of 2:00-8:00pm to control for the diurnal variations in blood pressure (Jones et al., 2008) with participants also completing a 4hr fast, 4hr abstinence from caffeine, and a 24hr abstinence from both alcohol and strenuous activity.

4.3 Part 1: The Theoretical Conceptualization and Experimental Analysis of the Maximal INTerval (MINT) Handgrip Protocol

4.3.1 Theoretical Conceptualization

The primary objective in designing the MINT exercise protocol was to select HG protocol design features that would enhance exercise accessibility by being simple to execute and easy to understand. In general, prescription of HG exercise commonly includes a combination of three protocol design features; (1) HG exercise intensity, (2) work-rest timing cycles, and (3) total exercise duration. The MINT protocol began with the selection of exercise intensity. Although HG exercise prescriptions using low to moderate MVC
intensities are commonly used, this design feature limits accessibility by requiring real-time force output during each exercise bout to regulate stimulus intensity. Alternatively, HG exercise can be prescribed at maximal grip force. Not only does this maximal effort negate the requirement for real-time force output data, it also self-calibrates over time as an individual’s grip strength increases thus allowing for extended periods of at-home training without frequent check-ins.

Using this maximal intensity grip force, a work-rest timing cycle and a total exercise duration had to be selected in order to provide an adequate stimulus to improve blood pressure while avoiding exaggerated cardiovascular (CV) responses that would affect the safety of the exercise for at-home use. For this, the literature was consulted as a first-step.

Maximal grip intensity exercise has been successfully used for at-home training among aged individuals with various work-rest timing cycles and total exercise durations. In a mixed-sex sample of older patients with chronic kidney failure, Kumar et al. prescribed HG exercise as maximal intensity with a 1sec-1sec work-rest timing cycle for a total of thirty minutes using a tennis ball (2010). Alternatively, in a mixed-sex sample of older individuals with and without chronic heart failure, Piepoli et al. prescribed HG exercise as maximal intensity with a 10sec-20sec work-rest cycle for a total of five minutes combined with five minutes of 40 grips/min using an in-house designed “gripper” (1995). Finally, in a mixed-sex sample of older patients with coronary artery disease, Lin et al. prescribed HG exercise as maximal intensity with a 1min-1min work-rest cycle for a total of forty minutes (twenty minutes each arm) using a non-specific dynamometer (2014). There was a considerable, yet controlled, systolic BP response during maximal exercise among participants with (rest ± SD to peak ± SD) chronic heart failure (128.1 ± 4.9 to 176.0 ± 25.3mmHg) (Piepoli et al., 1996), coronary artery disease (135.5 ± 12.8 to 142.6 ± 11.8mmHg) (Lin et al., 2014), and healthy control subjects (132.3 ± 5.1 to 189.6 ± 20.9mmHg) (Piepoli et al., 1996). However, these studies lack a combined assessment of the immediate cardiovascular reactions to the hand grip stimulus as well as quantification of the actual versus prescribed force outputs throughout the exercise bout. Given that acute physiological alterations brought on by an exercise bout are linked to long-term adaptations elicited by that training (Liu et al., 2012), the physiological responses to a maximal grip contraction and the underlying control of those alterations were considered when selecting the MINT work-rest timing cycle and the MINT total exercise duration. Since long-term HG training-induced reductions in resting BP are postulated to be mediated by both alterations to the autonomic nervous control of neurocardiac function and vascular structures and perturbations to local forearm blood flow (Lawrence et al., 2015; Millar et al., 2014), these were the regulatory factors that were isolated. Where possible, the physiological responses patterns of older women specifically were considered.
During an acute exercise bout, the autonomic nervous system acutely alters BP and HR via central command and the exercise pressor reflex (EPR), comprised of the mechanoreflex and the metaboreflex. Central command is a feedforward neural mechanism originating from the volitional intent to exercise which increases BP through both reductions of parasympathetic nerve activity and increases of sympathetic nerve activity (Ciriello et al., 1986; Goodwin et al., 1972; Krogh & Lindhard, 1913). It has previously been demonstrated that the influence of central command is not strongly associated with exercise intensity and is instead based on an individual’s sense of exercise effort, such as perceived exertion (Williamson et al., 2002). In contrast, EPR is a feedback peripheral neural system that originates in contracting skeletal muscle during an exercise bout with two groups of fibers that independently participate in the muscle mechanoreflex (group III fibers) and the muscle metaboreflex (group IV fibers) (Kaufman & Hayes, 2002). The mechanoreflex is rapidly stimulated by mechanical distortion of intramuscular receptors, proportional to the peak tension developed by the working muscle (Hayward et al., 1991; Kaufman et al., 1983; Mense & Stahnke, 1983). In static contractions, the discharge rate of group III fibers decreases as the working muscle fatigues, proportional to exercise intensities (Hayward et al., 1991; Kaufman et al., 1983). In comparison, the metaboreflex is stimulated by the chemical milieu produced by exercising muscle with notable metabolites such as [H+], [bradykinin], [K+], [lactic acid], and adenosine (Kaufman & Hayes, 2002; Murphy et al., 2011). Metabolite accumulation is amplified with prolonged static contractions at intensities that limit local blood flow to the working skeletal muscle, as seen in isometric contractions of >20% MVC (Barcroft & Millen, 1983; Barnes, 1980; Donald et al., 1967).

The conceptualization of the MINT exercise protocol considered all three of these neural regulatory pathways with careful consideration allocated to the specific responsiveness of these pathways among older women. Recent research has identified that older women have an overactive metaboreflex that is associated with enhanced peripheral vasoconstriction (Choi et al., 2012) as well as an overactive mechanoreflex (Park & Kim, 2011). Therefore, the MINT protocol design features were selected in an effort to minimize the influence of each branch of the EPR during the handgrip exercise bout. The mechanoreflex was minimized by limiting the time in grip contraction to only 5sec, as opposed to previously used durations of 10sec (Piepoli et al., 1996) and 1min (Lin et al., 2014). Young men and women completing a 5sec-5sec work-rest timing cycle have produced high intensity grip (50%MVCs) for more than thirteen minutes with high tolerability (Gonzalves et al., 2007). The metaboreflex was limited by incorporating rest periods of sufficient duration to facilitate the hyperaemic flow, providing adequate oxygenated blood and subsequently removing any metabolic by products.
With a maximal HG exercise intensity and a work-rest cycle of 5sec-5sec, the final protocol design feature to be selected was the total exercise duration. In line with the primary objective of enhanced accessibility, a shorter exercise duration was preferred while attempting to align the force-time integral of impulse between MINT and the commonly used sustained HG protocol of ZONA. Previous research using the ZONA automated digital grip device has reported that during an individual HG exercise bout participants are able to achieve high exercise compliance (97%, (Millar et al., 2011); 100%, (Badrov et al., 2013a); 95%, unpublished in-laboratory work). We anticipated a similar pattern of compliance to MINT and therefore aligned the calculation of impulse as:

\[
(ZONA \ N \ force) \times (ZONA \ time) = (MINT \ N \ force) \times (MINT \ time)
\]

\[
(30\% \ of \ maximum \ N \ force) \times (480s) = (90\% \ of \ maximum \ N \ force) \times (MINT \ time)
\]

\[
144 \ (\%N\cdot s) / 0.9 \ %N = (MINT \ time)
\]

160 seconds = MINT time

Therefore, the resulting final exercise prescription was 32 x 5 sec maximal grip squeezes separated by 5sec of rest in-between sets, resulting in a total protocol time of 5 minutes and 20 seconds.

In conclusion, the rationale for the design of the MINT exercise protocol was multi-factorial. First and foremost, the HG protocol was designed to be easy to understand and easy to execute. By prescribing exercise as maximal effort, the MINT protocol does not require the regulation of real-time force output and can therefore be completed without supervised laboratory visits or specialized at-home exercise equipment. Prior to initializing at-home exercise training, it is imperative that the MINT exercise protocol be experimentally analyzed to quantify performance, describe the acute cardiovascular responses, and determine participant feedback.

4.3.2 Experimental Analysis

The experimental analysis of the MINT exercise protocol occurred as two sequential investigations. Maximal HG exercise carried out by older, otherwise healthy, normotensive women as part of a larger physiological comparison study (Chapter 3). Secondly, maximal HG was performed by older women with above optimal resting BP and various co-morbidities and medication use as part of a long-term training study (Chapter 5).

Purpose: Within each group of women, the experimental purpose was to: (1) quantify handgrip performance while completing the MINT protocol, (2) describe the acute cardiovascular responses to
Methodology: The experimental visits for the assessment of the physiological responses to MINT exercise were similar for the two cohorts of older women. Participants arrived at the laboratory, completed paperwork (restriction compliance quiz (Appendix 2e), STAI (Spielberger et al., 1982)(Appendix 2d), and began 15 minutes of seated rest with the right arm supported at heart level. During the last 10 minutes, resting cardiovascular measurements were taken simultaneously by two devices; a BpTRU oscillometric blood pressure cuff on the left arm recorded SBP, DBP, and heart rate (HR) values once every two minutes (six total readings), and a Finometer photoplethysmograph finger cuff on the middle phalanx of the third digit recorded beat-to-beat values of SBP, DBP, and HR. While supported in this same seated position, participants completed HG exercise with a grip dynamometer (ADI Instruments) using their non-dominant hand (left for all) while the Finometer recorded the during-exercise responses of BP and HR. A timed PowerPoint presentation guided participants through the prescribed protocol timing of 32x5sec contractions a with 5sec rest in between sets. All grip contractions were to be completed at maximal strength. Participants verbally indicated their rating of perceived exertion (RPE: 6-20 scale) at the midway point and at the end of the exercise bout (Borg, 1982). Following exercise cessation, participants in the initial cohort only (healthy normotensive women) remained in the seated position for thirty minutes of recovery while post-exercise recovery of BP and HR were recorded (BpTRU) every three minutes.

To quantify HG performance while following the MINT protocol, real-time force data was collected (LabChart, 2010) throughout the duration of exercise, converted into per-second outputs, and an intensity percentage calculated using an individual’s one repetition maximum (1RM) values. 1RM values were determined as the maximum 1sec force output from three consecutive 5sec holds during the baseline visit. Force performance is expressed as the average performance throughout the working time as well as the logarithmic decline in strength over time. To describe the during-exercise cardiovascular responses, SBP, DBP, and HR were collected as beat-to-beat data, converted into change scores from day-of rest, and calculated as both an average change value (denoted throughout as “Avg”) and a peak 5sec change value (denoted throughout of “Peak”). To collect participant feedback, RPEs were acquired at the midway point and at the end of the exercise bout. Additional feedback from participants was collected in two ways. The initial cohort of healthy normotensive women completed online surveys (Appendix 2f) where they rated (1-10 scale ) if they enjoyed the exercise protocol, if the protocol was easy, and if the protocol was fatiguing.. Net Promoter Scores are calculated using the answer to a single question, with a 0-10 scale:
How likely is it that you would recommend [brand] to a friend or colleague? Respondents were grouped into Promoters (9-10), Passives (7-8) and Detractors (0-6). Subtracting the percentage of Detractors from the percentage of Promoters yields the Net Promoter Score, which can range from a low of -100 (if every customer is a Detractor) to a high of 100 (if every customer is a Promoter) (Eastman, 2015). This feedback regarding the MINT protocol was compared to feedback regarding the ZONA protocol (acquired during a different experimental visit on an alternative day) to determine relative acceptability. The subsequent cohort of women with above optimal BP provided open-ended feedback regarding the exercise protocol at the end of the experimental visit. Finally, statistical correlations were run to assess potential ANS drivers of the instantaneous cardiovascular reactivity.

Results: The initial cohort (NT women) was comprised of twenty older (57.7 ± 5.2yrs), post-menopausal (8.4 ± 5.6yrs) women with optimal resting cardiovascular measures (SBP: 109.1 ± 9.1mmHg, DBP: 73.3 ± 7.7mmHg, HR: 71.5 ± 7.0bpm) who self-reported to be active (RAPA: 7.4 ± 2.1) and free from co-morbidities. The subsequent cohort was comprised of eleven older (62.5 ± 3.9yrs), post-menopausal (8.1 ± 5.1yrs) women who self-reported to be moderately active (RAPA: 6.0 ± 2.4), with various co-morbidities including pre-hypertension (n=7, two on BP medication), hypertension (n=4, two on BP medication), arthritis (n=2), Raynauds (n=1), diabetes (n=1), osteoporosis (n=1), asthma (n=2), arterial fibromuscular dysplasia (n=1), and palmer fibromatosis (n=1). All participants in this cohort (AO women) presented with above-optimal resting cardiovascular measures (SBP: 134.3 ± 12.5mmHg, DBP: 80.6 ± 9.4mmHg, HR: 73.7 ± 8.0bpm).

All participants were successfully able to complete the full MINT exercise protocol without experiencing any clinical abnormalities or inappropriate symptoms during or immediately after the MINT exercise protocol. As is typical during HG exercise, some (n=4) participants commented on mild to moderate fatigue in the forearm finger flexor muscles. Among the initial cohort, maximal grip over the full session duration translated to an average force of 50.4% with the change in force overtime characterized as a natural logarithmic decline \(y = -6.4ln(x) + 80.92, \ R^2 = 0.59\) (Figure 4.1a). This HG performance was confirmed in the subsequent cohort with maximal grip translating into an average force of 49.7% and change in force overtime characterized as a natural logarithmic decline over the exercise bout \(y = -7.3ln(x) + 84.2, \ R^2 = 0.64\) (Figure 4.1b).

As expected, both groups of women demonstrated pronounced cardiovascular responses to the MINT exercise protocol exemplified through both the average and peak change scores. Among NT women, MINT handgrip exercise elicited elevations in SBP (Avg: 24.1 ± 12.0mmHg, Peak: 42.2 ± 14.3mmHg),
Figure 4.1. Grip Performance Over The Duration of the MINT Exercise Protocol. Panel A: initial protocol analysis in a cohort (n=20) of otherwise healthy, normotensive, post-menopausal women. Panel B: subsequent protocol analysis in a cohort (n=11) of post-menopausal women with above-optimal resting BP.
DBP (Avg: 10.9 ± 6.7mmHg, Peak: 21.2 ± 8.1mmHg) and HR (Avg: 4.8 ± 4.5, Peak: 13.8 ± 7.1mmHg). Following cessation of exercise all CV variables returned to day-of resting values immediately, and remained at rest for the 30 minute post-exercise duration (Figure 4.2). In comparison, among the AO women a statistically significant response to the MINT exercise only occurred for SBP (Avg: 23.2 ± 19.8mmHg, Peak: 40.9 ± 18.2mmHg). Acute responses of DBP (Avg: 3.9 ± 15.5mmHg, Peak: 18.9 ± 16.5mmHg) and HR (Avg: -2.6 ± 6.4, Peak: 21.3 ± 15.0mmHg) did not reach significance (Figure 4.3). (Mean±SEM) Although the absolute average SBP value during HG exercise was greater in the AO cohort (NT: 132.2 ± 4.0mmHg, AO: 157.1 ± 6.0mmHg, p<0.05), this difference can be attributed to augmented resting values since there was no difference in SBP increase between the cohorts (NT: 24.1 ± 2.7mmHg, AO: 23.2 ± 5.9mmHg, p>0.05). In comparison, absolute DBP values of the cohorts reached similar absolute levels (NT: 83.5 ± 2.0, AO: 84.3 ± 5.6, p>0.05) despite different resting values (NT: 72.6 ± 1.9mmHg, AO: 80.6 ± 2.8mmHg, p<0.05), due to trending change scores (NT: 10.9 ± 1.5, AO: 3.9 ± 4.7, p= 0.069). Resting HR between the two cohorts was similar (NT 71.2 ± 7.0bpm, AO: 73.7 ± 2.4bpm, p <0.05), however, the response to HG differed significantly (p < 0.01) with reduced HR for the AO group (AO: -2.6 ± 1.9bpm) and increased for the NT ((NT: 4.8 ± 1.0bpm) (Figure 4.3).
Figure 4.3. A Direct Comparison of the Cardiovascular Responses to MINT for Normotensive Women (NT) and Women with Above-Optimal Resting Blood Pressures (AO). Difference from resting † p<0.05, Difference from NT # p<0.05, Difference between change scores ** p<0.01.
Ratings of perceived exertion were similar between cohorts at both the midway (NT: 12.9 ± 2.6, AO: 13.6 ± 1.4) and end (NT: 13.5 ± 2.9, AO: 14.8 ± 2.5) of HG exercise with an average RPE of (NT:13.2 ± 2.7, AO: 14.2 ± 2.0). Exit surveys completed by the NT group revealed that participants found the MINT protocol to be less enjoyable (MINT: 5.3 ± 2.5, ZONA: 8.03 ± 1.4, p<0.05), not as easy (MINT: 6.0 ± 2.8, ZONA: 7.9 ± 2.0, p < 0.01), with an insignificant difference in resulting fatigue (MINT: 5.1 ± 2.7, ZONA: 4.3 ± 2.8, p > 0.05). In line with these opinions, only 25% of participants indicated that they would promote the MINT protocol to a friend and/or colleague, versus 75% that indicated they would promote the ZONA protocol. In the AO group, only one participant provided additional qualitative feedback on the MINT protocol directly say that “it was easy”-LT14.

Among the NT group there was a strong correlation between individuals’ MINT exercise grip performance and their corresponding average responses of SBP (r=0.53, p<0.05), DBP (r=0.55, p<0.05), and HR (r=0.65, p<0.01) that was not replicated in the AO group. Cardiovascular responses to exercise were not correlated with any other variable, including exercise RPE, age, body mass index (BMI), resting SBP, or year since last menstrual period (YLMP).

Context: As expected, HG exercise performance was lower than the prescribed 100%MVC. On average, participants exerted a grip force equivalent to approximately half of their 1sec average (NT: 50.4%, AO: 49.7%). Although the high intensity MINT exercise caused substantial cardiovascular responses, the resulting 5sec peak responses of SBP (NT: 150.3 ± 20.1mmHg, AO: 175.2 ± 20.6mmHg) and DBP (NT: 89.6 ± 9.5mmHg, AO: 99.4 ± 20.1mmHg) remain far below the thresholds of concern identified by the ACSM (SBP: >250mmHg, DBP: >115mmHg) (American College of Sports Medicine, 2013). The potential impact of medication use on BP response to HG exercise was determined within the AO group as there were a total of four women controlling their BP with ACE inhibitors (n=2), calcium channel blockers (n=1), or diuretics (n=1). Additional statistical analysis revealed a significant impact of medication use on the instantaneous DBP response, with those taking medication presenting with an enhanced response (15.1 ± 16.5mmHg) and those not taking medication displaying a reduction (-2.8 ± 8.7mmHg) (p<0.05). There were no differences in the during-exercise responses of SBP (30.7 ± 22.3mmHg versus 18.4 ± 13.2mmHg, p>0.05) and HR (+1.27 ± 7.8bpm versus -4.9 ± 3.2bpm, p>0.05). Future research, with adequate statistical power, is required in order to properly assess the impact of BP medication on the acute cardiovascular response to HG exercise.
Collectively, the MINT protocol feedback appears discouraging. However, further analysis of participant comments reveals that the discomfort of having to use the ADI Instrument as the grip tool during the MINT protocol may be driving some of the negative reviews. “The texture of the devices is enormously different and influences one’s response to both the device and the protocol” – ST09. “The ZONA protocol was frustrating to keep squeeze constant but it was still more enjoyable than the cold steel, hard to hold, [ADI] tool” – ST15. As such, interpretation of the protocol feedback is not straightforward. Given that participants only experienced moderate ratings of perceived exertion, and comparable levels of muscular fatigue, the decision was made to shift research attention towards the grip tool directly.

### 4.3 Part 2: New Product Development: the Maximal INTerval Handgrip Tool

During the experimental assessment of the MINT exercise protocol, feedback from participants indicated that the in-laboratory grip tool (ADInstruments) was unpleasant and uncomfortable. Ultimately, the negative influence of the tool was impacting the overall exercise opinions and presented us with an opportunity to develop a grip tool that would be more acceptable for HG exercise training.

The process of New Product Development (NPD) identifies activities commonly employed when creating and launching new products. Before introducing a product the initial product idea has been evaluated, developed, tested, and launched (Booz, Allen & Hamilton, 1982). Although several detailed NPD models have been conceptualized and tested over the years, the original model put forth by Booz, Allen and Hamilton (Booz, Allen, & Hamilton, 1982) is the most well-known and widely used (Bhuiyan, 2011), consisting of seven sequential stages including a final “commercialization” stage. However, the current research objective is driven by knowledge generation and is not concerned with the commercialization of a product for retail. Therefore, only the pre-commercialization development processes have been presented and discussed (Bhuiyan, 2011).

The product idea for a MINT grip tool presented itself as a result of feedback from research participants. As previously described, when asked to provide feedback regarding the MINT exercise protocol participants’ overwhelming discontent with the ADInstrument grip dynamometer (aka, the ADI tool) was overshadowing their responses regarding the exercise protocol. During those aforementioned experimental visits formal feedback was also collected regarding the grip tool directly.
4.4.1 Leading into the Design and Development Stage of the MINT Tool Development

Research Methodology: During the experimental analyses of the MINT exercise protocol, both normotensive women (n=20) and women with above-optimal resting BP (n=11) used the ADI tool for in laboratory completion of the MINT exercise protocol. This metal tool has a rectangular shape (12.8 cm circumference), and weighs 287.7g. The NT women completed a HG exercise bout on a separate research day using an alternative exercise strategy; ZONA. The ZONA protocol consists of 4x2min sustained grip squeezes at 30%MVC with 1min of rest in between and the ZONA tool has a contoured shape (15.5cm circumference), and weighs 162.7g (Table 4.2). As part of an exit survey (Appendix 2f), the normotensive women rated (1-10 scale) each tool for enjoyment, comfort, and provided independent Net Promoter Scores (10 point scale from 1-10). Participants also had the opportunity to provide open-ended feedback regarding the grip tools. The AO cohort provided open-ended feedback regarding the ADI tool only at the end of the experimental visit.

Results: Normotensive participants (NT) had greater enjoyment using the ZONA tool (8.1 ± 1.8) versus the ADI tool (5.0 ± 2.6) (p<0.01), and greater comfort using the ZONA tool (9.0 ± 0.9) versus the ADI tool (4.4 ± 2.6) (p<0.01). In line with these opinions, only 35% of participants indicated that they would promote the ADI tool to a friend and/or colleague, versus 90% that indicated they would promote the ZONA tool. A total of 14 women (70%) chose to provide qualitative feedback on what would make
an ideal handgrip tool, combined with feedback from the 11 AO women. Thematic assessment of open-end comments from both groups revealed 4 primary areas: real-time feedback, grip material, physical shape, and circumference size. Two of the women expressed a desire for real-time digital feedback regarding grip force performance (n=1) and time remaining (n=1). Unfortunately, given that the overall purpose of this research is to design a simple and accessible handgrip tool we are unable at this time to incorporate a real-time feedback component. With regard to grip material, many thought that a softer (n=8) grip with texture (n=3) was desirable, with comfort (n=3) and grip responsiveness (n=2) as items to consider when creating an at-home grip tool. Finally, participants suggested that the tool have an ergonomic shape (n=2) that is not too heavy (n=1) with a smaller circumference size (n=3).

**Perspectives:** With the discontent towards the ADI grip tool and the associated participant suggestions, four mock-MINT grip tools were constructed from simple materials. The four mock-MINT grip tools varied in size, shape, grip covering, and colour and were assessed during focus groups to determine participant preferences and ratings of acceptability.

### 4.4.2 The Testing Stage of the MINT Tool Development

**Purpose:** To determine participant preferences and ratings of acceptability regarding four mock-MINT tool prototypes and two in-laboratory tools.

**Research Methodology:** Four MINT grip prototypes were created that incorporated various suggestions from previous participants. The tool characteristics are summarized in Table 4.2. Older women from the community gave their feedback during small focus groups by ranking and rating all six grip tools (Appendix 2g) regarding all six tools: the ADI dynamometer, the ZONA dynamometer, and the 4 mock-MINT tool prototypes. Participants were asked to rate (using a 50 point scale from 0-(The Worst) to 10-(The Best)) the tool features of colour, shape, size, and grip of each tool. They were also asked to use the Net Promoter Scale to indicate how likely they would be to recommend this tool, with its current combination of features, to a friend. To conclude the focus group session, participants were asked to select their top choice of colour, shape, size, and foam grip. Before leaving, the hand size of each participant was determined by measuring from the most distal tip of the third digit to the natural proximal wrist crease (approximately the distal edge of the radius). Participant ratings of the HG tools were statistically compared using a 6 (tools) x 4 (factors) two-way analysis of variance (ANOVA) with repeated measures, followed by multiple one-way ANOVAs with Bonferroni corrections as necessary. Additional correlations were completed to assess relationships between factors.
<table>
<thead>
<tr>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>mock-MINT Tool 1</strong></td>
</tr>
<tr>
<td>- Black colour</td>
</tr>
<tr>
<td>- Rectangular (rounded edges)</td>
</tr>
<tr>
<td>- 12cm central circumference</td>
</tr>
<tr>
<td>- “Supercycle Foam Handlebar Grip”</td>
</tr>
<tr>
<td><strong>mock-MINT Tool 2</strong></td>
</tr>
<tr>
<td>- Grey and black colour</td>
</tr>
<tr>
<td>- Ergonomically contoured with a round central core</td>
</tr>
<tr>
<td>- 10.5cm inner, 12cm central, 12.5cm outer circumferences</td>
</tr>
<tr>
<td>- Schwinn Double-Layer Gel Comfort Bike Grips</td>
</tr>
<tr>
<td><strong>mock-MINT Tool 3</strong></td>
</tr>
<tr>
<td>- Yellow Colour</td>
</tr>
<tr>
<td>- Rectangular</td>
</tr>
<tr>
<td>- 10.5cm central circumference</td>
</tr>
<tr>
<td>- Wilson Pro Overgrip (tennis)</td>
</tr>
<tr>
<td><strong>mock-MINT Tool 4</strong></td>
</tr>
<tr>
<td>- Pink colour</td>
</tr>
<tr>
<td>- Rectangular</td>
</tr>
<tr>
<td>- 10.5cm central circumference</td>
</tr>
<tr>
<td>- Tacki-Mac Command Hockey Grip Slider</td>
</tr>
<tr>
<td><strong>ADI Instrument</strong></td>
</tr>
<tr>
<td>- Grey Colour</td>
</tr>
<tr>
<td>- Rectangular</td>
</tr>
<tr>
<td>- 12.8cm central circumference</td>
</tr>
<tr>
<td>- Metal</td>
</tr>
<tr>
<td><strong>ZONA</strong></td>
</tr>
<tr>
<td>- Grey and beige colour</td>
</tr>
<tr>
<td>- Ergonomically contoured</td>
</tr>
<tr>
<td>- 15.5cm central circumference</td>
</tr>
<tr>
<td>- Plastic</td>
</tr>
</tbody>
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Table 4.2. Summary of Grip Tool Design Features for the New Product Development Focus Groups.

**Results:** Twenty older women from the community volunteered to participate in focus groups. Participants were a combination of women who were new to our laboratory facilities (n=9) and those who had previously completed other HG exercise research training studies (n=11). Two-way ANOVA revealed a significant interaction effect between tools and factors (p<0.01) with corresponding post-hoc comparisons revealing a robust preference for mock-MINT prototype #1 for both shape and grip (Figure 4.4). When forced to select only one tool for each of the assessed grip tool factors, mock-MINT prototype...
#1 was consistently selected the majority of the time for all factors (Size: 55%, Shape: 50% Colour: 45%, Grip: 50%), achieving an extremely high NPS ranking with 75% of women indicating that they promote this tool to a friend. Mock-MINT prototype #2 was the runner up for all tool factors (Size: 25%, Shape: 30%, Colour: 25%, Grip: 40%), with 50% of women indicating that they would promote this tool to a friend. Hand size was not correlated with tool size ratings for any of the tools. Of particular interest, both of the in-laboratory HG tools rated particularly low among focus group participants. Although there are aspects of each that make them strong research tools, such as real-time grip force data (ADI instrument) and set training parameters (ZONA), their design features were rated extremely low and they also received very low NPS ratings of 0% and 5%, respectively.

Figure 4.4 Feedback from the New Product Development Focus Groups. As compared to Tool 1, *p<0.05 **p<0.01

**Perspectives:** This research represents the testing stage of NPD where six handgrip tools were directly compared and assessed by focus groups of older women from the community. Although it was unanticipated that one tool would be favoured across all tool dimensions, focus group participants displayed strong preferences for all the design features of the mock-MINT tool #1, including colour, shape, size, and foam grip. As such, tool #1 with its current design features and high degree of population acceptability was selected as the MINT handgrip tool.
4.5 Collective Discussion

This research describes the thorough and methodical development and assessment of the Maximal INTerval handgrip exercise strategy. The MINT handgrip exercise protocol was theoretically driven to be highly accessible and easy to follow. It was first experimentally assessed among a cohort of otherwise healthy older women and was found to be both low risk (as determined by measuring both BP and HR reactions and post-exercise cardiovascular recovery) and tolerable (as determined through participant opinions and measures of exercise performance). The MINT exercise protocol was subsequently assessed among a cohort of women with above-optimal BP and was confirmed to be risk-free and tolerable. In addition to the MINT handgrip exercise protocol, this research also describes the development of a new product: the MINT grip tool. Research participants initially provided structured feedback regarding two in-laboratory devices which led to the design of four mock-MINT tools. Structured focus groups were conducted to collect participant opinions and inform the final MINT grip tool design. Together the MINT handgrip exercise protocol and the MINT grip tool represent a tested, highly accessible, easy to use, participant-informed handgrip exercise strategy which has the potential to be utilized for at-home training interventions. By purposefully including the opinions of research participants in the MINT development process, we are confident that the resulting MINT handgrip strategy represents an accessible exercise form that this cohort of individuals can adequately complete at home while experiencing cardiovascular responses that fall within safe and reasonable limits.

A strength of this design was the directed research attention towards our target population; older women. As women age their risk of cardiovascular disease increases fourfold after the menopause transition (Yang & Reckelhoff, 2011). Controlling CVD risk-factors, such as resting blood pressure, can mitigate the impact of CVD, as more than 50% of all CV diseases are directly related to high BP (World Health Organization, 2013a). Handgrip exercise training has been used in the health literature as a strategy to effectively reduce BP with a surprising lack of research regarding sex-specific HG-induced BP reductions. Furthermore, there is minimal sex-specific research regarding the potentially disparate physiological responses to various design features (ie. intensity, duration of static contraction, work-to-rest ratios, etc.) of handgrip exercise protocols. During sustained isometric handgrip contractions women, compared to men, experience longer endurance times and less fatigue across a range of grip intensities from 30-75% MVC (Petrofsky, Burse, & Lind, 1975; West, Hicks, Clements, & Dowling, 1995). In contrast, during intermittent (5sec contraction, 5sec relaxation) HG exercise at 50%MVC intensity, the sex-dependent differences in grip performance and fatigue disappear (Gonzalves et al., 2007). In further
examining the sex-dependent responses to intermittent handgrip exercise, the physiological impact of autonomic nervous system function may help elucidate some of the rationale for different responses.

The Maximal INTerval handgrip exercise protocol was designed with the specific autonomic responses of older women in mind. This refers to the feed-forward central command, and the two types of reflex exercise presser responses, mechanoreflex and the metaboreflex. Although the current research was not designed to explicitly determine the individual influence of each neural pathway on the instantaneous cardiovascular reactivity to MINT exercise, simple ad-hoc correlations to explore relationships between variables may help inform future research designs. For example, the influence of central command can be estimated by examining the correlation between an individual’s rating of exercise exertion and their corresponding BP response, while the influence of the mechanoreflex can be estimated by examining the correlation between an individual’s handgrip intensity output and their corresponding during-exercise BP response. Among the NT women studied in the initial experimental assessment of MINT, there was no significant correlation between RPE scores and average SBP, DBP and HR reactivity, indicating an insignificant influence of central command. Furthermore, among NT women there was a significant correlation between performed grip intensity and average instantaneous changes in SBP (r=0.53, p<0.05), DBP (r=0.55, p<0.05), and HR (r=0.65, p<0.01), indicating that the CV reactivity during MINT handgrip exercise is likely being driven by mechanoreflex. Since sustained isometric grip squeezes were avoided and instead the MINT protocol was theoretically designed to promote local forearm blood flow, the metaboreflex was likely not a strong driving factor. This response pattern is not mirrored among the AO women studied in the subsequent experimental analysis of MINT who, alternatively, displayed no significant correlations of average CV reactivity to either RPE scores or performed grip intensity. Since neither indicators of central command nor indicators of mechanoreflex are driving the CV responses during MINT in the AO group, it is reasonable to assume that perhaps the metaboreflex is driving the BP responses despite efforts to avoid metabolite accumulation. In a study of older adults, enhanced metaboreflex sensitivity is reported among individuals with above-optimal resting BP with significant difference in the response of SBP to post-exercise ischemia (12±3mmHg versus 6±1mmHg) (Sausen, Delaney, Stillabower, & Farquhar, 2009). Perhaps the MINT protocol is effective in reducing, but not eliminating, local metabolite accumulation. Research with the primary goal of determining the particular ANS responses to handgrip exercise among these two groups of women is required to confirm current speculations. It would be extremely useful if such research also included older men for sex-specific comparisons of the ANS-driven pressor response to exercise.
**High Intensity Grip Safety:** Isometric exercise produces an acute pressure load on the heart by raising SBP and DBP spanning the duration of the exercise bout. The large BP responses have resulted in concerns regarding isometric exercise, especially in hypertensive populations (Chrysant, 1978; Mitchell & Wildenthal, 1974). In response to these concerns, the American College of Sports Medicine recently published guidelines that identify concerning exercise BP values of 250mmHg systolic and 115mmHg diastolic (American College of Sports Medicine, 2013). With these guidelines in mind, the current research used continuously collected BP and HR data to determine the cardiovascular response to high intensity handgrip exercise using a conservative approach of identifying 5sec peak values. It was first determined that healthy normotensive women completing high-intensity interval handgrip exercise experienced peak BP responses below these published guidelines (150.3/89.6mmHg). High intensity handgrip exercise was subsequently introduced to a cohort of women with above-optimal resting BP, confirming that CV responses during high intensity HG exercise (175.2/99.4mmHg) remained well below threshold values. Future researchers should be confident in employing the MINT handgrip exercise training protocol for at-home or unsupervised use among older women with resting BPs that extend into the classification of Stage 1 of hypertension.

**Health Behaviour:** Changes in health behaviour can be difficult to encourage. Research in the field of health behaviour change has attempted to circumnavigate this barrier by establishing incentive programs (Giles, Robalino, McColl, Sniehotta, & Adams, 2014) and developing robust interventions for both single health behaviour change and multiple health behaviour change (Nigg & Long, 2012). Researchers who have employed HG exercise have reported uncharacteristically high adherence with very little participant drop-out. One reason for this noted adherence may be that handgrip exercise requires relatively little time as compared to traditional aerobic resistance training programs. The MINT protocol requires just over 5 minutes a day, approximately 1/5th the recommended daily aerobic duration. Handgrip exercise may lead to successful exercise adherence and clinically significant BP reductions. However one disadvantage of HG exercise is that we know very little about the secondary health outcomes that commonly accompany traditional whole body programs (ie. improved blood lipid profile, alterations of body fat, etc.). Future research with the primary outcomes of assessing such secondary variables would be useful.
CHAPTER 5

Maximal Interval Handgrip Exercise Training Lowers Resting Blood Pressure and Increases Heart Rate Complexity among Older Women

5.1 Introduction

There is a growing body of review literature substantiating the use of isometric handgrip (HG) exercise training for blood pressure reduction (Carlson et al., 2014; Lawrence et al., 2015; Millar et al., 2014). Specifically, recent meta-analysis data indicates that in randomized controlled trials the impact of at least 4 weeks of HG training is clinically substantial for both SBP (Mean [95%CI]) (-6.8mmHg [-7.9 to -5.6]) and DBP (-3.9mmHg [-4.8 to -3.1]) (Carlson et al., 2014). The recently demonstrated clinical efficacy of HG exercise aligns well with expressed desires from both patients’ and clinicians’ for therapeutic research attention to shift focus towards non-pharmaceutical treatment options (Crowe et al., 2015).

The health benefits associated with alternative lifestyle interventions, such as exercise programs, can be especially impactful for the aging population (Chodzko-Zajko et al., 2009). Unfortunately, despite compelling scientific research and widespread public health recommendations, among women 45–64 years and 65–74 years old, only 18% and 11%, respectively, perform physical activities that enhance and maintain muscle strength and endurance two or more times per week (Kruger et al., 2007). Among those who decide to adopt an exercise program, the aging population frequently displays a very low level of adherence (van Heuvelen et al., 2006), with approximately 50% of people who begin an exercise program discontinuing that program within six months (Hong, Hughes, Prohaska, 2008; Medina-Mirapeix, Escolar-Reina, Gascon-Canovas, Montilla-Herrador, & Collins, 2009; Kallings, Leijon, Kowalski, Hellenius, & Stahle, 2009). This can be problematic when exercise is being used for therapeutic use, especially when an adherence level of at least 80-85% is recommended if the results of an intervention are to be satisfactory (Pisters et al., 2010). In the aging population specifically, adherence diminishes over time (Pisters et al., 2010) with lower exercise compliance for aerobic training regimens as compared to resistance training regimens (Hong et al., 2008; Picorelli et al. 2014). With the noted adherence challenges, ideal exercise options for this population should be both efficacious (able to produce the desired clinical outcomes under tightly controlled research restrictions) and effective (able to replicate desired outcomes under “real world” settings without research restrictions, includes considerations of exercise program adherence).
Although the handgrip literature generally indicates promising exercise adherence, these values may be misleading as the vast majority of the HG training literature are efficacy trials that use supervised laboratory sessions for training. Few researchers have identified the exercise adherence of individuals completing unsupervised HG training. Among a mixed-sex sample of older adults completing ten weeks of HG exercise (two out of three training sessions per week were at-home) there was a reported exercise adherence score of 100% (Badrov et al., 2013b). The same research group again reported 100% exercise adherence to eight weeks of HG exercise (three out of five training sessions per week were at-home) (Badrov et al., 2013a). Finally, although in a sample of younger men, adherence of ≥ 90% was reported to four weeks of high intensity intermittent HG exercise (Allen et al., 2003). Research that utilizes unsupervised at-home HG training programs with exercise behaviour outcomes is required to validate this seemingly high exercise adherence to HG exercise.

Therefore, this research was designed to assess both the physiological efficacy and behavioural effectiveness of the Maximal INTerval (MINT) handgrip strategy. The MINT strategy includes the MINT exercise protocol and the MINT grip tool, both of which were created and tested in our laboratory (Chapter 4). First and foremost, the MINT exercise protocol was designed to be easy to understand and easy to execute. By prescribing exercise as maximal intensity, the MINT protocol does not require the regulation of real-time force output and can therefore be completed without supervised laboratory visits or specialized at-home exercise equipment. Previous research conducted within our laboratory has analyzed the acute physiological responses of older women to the MINT exercise protocol and determined that not only do peak 5sec average cardiovascular responses SBP (NT: 150.3 ± 20.1mmHg) and DBP (NT: 89.6 ± 9.5mmHg) remain far below the thresholds of concern identified by the ACSM (SBP: >250mmHg, DBP: >115mmHg) (American College of Sports Medicine, 2013), but exercise-induced cardiovascular responses dissipate quickly following exercise cessation (Chapter 3). Grip performance while following the maximal intensity exercise protocol has also been previously analyzed, with an average relative force production throughout the MINT exercise protocol of 50.4% of maximal volitional contraction (MVC) (Chapter 3). As a natural extension of this preliminary research, the MINT handgrip exercise strategy will be further validated among a cohort of older women through the assessment of exercise efficacy and exercise effectiveness.

In agreement with a proof of concept methodology, this research is designed as a prospective cohort design with two research objectives. The primary research objective was to explore the physiological efficacy of MINT exercise training by assessing cardiovascular alterations resulting from an 8week
training intervention. Cardiovascular alterations of interest included resting systolic BP, diastolic BP, and HR. Additional physiological variables of interest included those that have been proposed as mediators of BP changes; a neurocardiac index of autonomic nervous control (heart rate variability (HRV)), and indicators of arterial structure (radial augmentation index (AIx), and carotid-radial pulse wave velocity (crPWV). Based on previous success of HG exercise interventions (Carlson et al., 2014) it was hypothesized that high intensity HG exercise training would reduce resting BP with an associated shift in heart rate complexity (Badrov et al., 2013b; Miller et al., 2013) in the absence of altered arterial structure. The secondary research objective was to explore indicators of behavioural effectiveness including at-home exercise adherence patterns, Physical Activity Enjoyment Scores, and qualitative indicators of anticipated/actual barriers to exercise. Based on previous success of at-home HG exercise training to high intensity HG exercise (Allen et al., 2003) it was hypothesized that although participants would anticipate exercise barriers pertaining to the themes of time and habit, they would nonetheless demonstrate high adherence to MINT exercise.

5.2 Methods

This study was approved by the Research Ethics Board at the University of Toronto (REB#31450) and is in accordance with the guidelines set forth by the Declaration of Helsinki (World Medical Association, 2013). Participants provided written informed consent after receiving a full explanation of all experimental procedures, exercise protocols, and possible risks associated with participation in the study. All testing was performed in an isolated room (free from external noise and distractions) within the Human Health and Performance Laboratory at the University of Toronto between the hours of 2:00-8:00pm to reduce the impact of diurnal variations in blood pressure (Jones et al., 2010). To limit external perturbations to BP, prior to each experimental visit participants completed a bladder void (Fagius & Karhuvaara, 1989), a 4hr fast, a 4hr abstinence from caffeine, and a 24hr abstinence from both alcohol and strenuous activity.

Participants: Participants were recruited from the greater Toronto area using online and word-of-mouth communication strategies. Inclusion criteria were kept broad for enhanced applicability and included: post-menopausal (≥ one year since last menstrual bleed), without current/previous use of hormone therapy medication, resting systolic blood pressure >115mmHg. Exclusion criteria were: current or previous cardiovascular disease (other than hypertension), current smokers, otherwise unable to participate in non-dominant handgrip exercise (ie. severe osteoarthritis, hand injury, etc.).
Research Design: This study was a prospective exercise intervention where all enrolled women completed eight weeks of at-home unilateral (non-dominant arm) handgrip exercise training. This pilot research was designed to precede a large randomized controlled trial and while there was no formally designated control group, comparisons were completed against the untrained arm as an intra-individual control, when appropriate. In addition to the at-home training, full study completion also included four visits to the Human Health and Performance laboratory. The first “familiarization” visit was to screen participants for inclusion criteria and to familiarize participants to the laboratory, the experimenter, the exercise protocols, and the laboratory equipment. During the familiarization visit participants completed mock laboratory procedures where data was recorded but not analyzed. The remaining three experimental visits were completed at the Baseline (day=0), Midway (day = 28 ± 2days), and End (day = 56 ± 4days) of an eight week high intensity HG exercise training intervention.

Experimental Visit Structure and Laboratory Assessments: For each of the three experimental visits the same general procedures were followed. Upon arrival at the laboratory participants were fitted with a chest strap and synchronized wrist watch for continuous collection of heart data (Sunnto, later replaced by Polar). Anthropometric measures of height, weight, and forearm circumference were recorded and participants then completed relevant paperwork including the Physical Activity Readiness Questionnaire Plus (first experimental visit only)(Warburton et al., 2011)(Appendix 2a), Rapid Assessment of Physical Activity (RAPA)(Topolski et al., 2006)(Appendix 2b), the State-Trait Anxiety Inventory (STAI)(Spielberger et al., 1970)(Appendix 2d). Participants transitioned to a seated and supported position for assessments of resting blood pressure, resting heart rate, and resting heart rate variability. An automated oscillometric brachial cuff (BpTRU Vital Signs made by Medical Devices, model #BPM-100, BC Canada) was positioned on the left arm for discontinuous BP and HR recordings. Simultaneously, the right arm was supported at heart level and fitted with a photoplethysmographic finger cuff (Finometer MIDI made by Finapres Medical Systems, model#2, Arnhem Netherlands) on the middle phalanx of the right third digit for beat-to-beat recordings of BP and HR. The timing sequence of seated rest progressed as: 5 minutes rest (no data collection), 10 minutes of day-of resting data collection (BpTRU recording once every two minutes, Finometer recording beat-to-beat values of BP and HR). Following resting assessments participants transitioned to the supine position for bilateral measurements of radial augmentation index and carotid-radial pulse-wave velocity. To conclude the experimental visit participants returned to the seated position, were re-fit and re-calibrated with the Finometer on the middle phalanx of the right third digit, and completed a bout of MINT handgrip exercise using an ADInstrument grip dynamometer as a substituted in-laboratory grip tool. As an exit survey, all participants completed an open-ended Questionnaire of Exercise Barriers (Appendix 2h), designed to acquire opinions regarding
perceived/anticipated barriers to MINT exercise (first visit) and actual/experienced barriers to MINT exercise (last visit).

**Resting Cardiovascular Measures:** The BpTRU brachial cuff recorded SBP, DBP and HR every two minutes for the final 10 minutes of seated rest. Of these 6 recordings, the highest and lowest values were dropped, and the remaining 4 values averaged. This BpTRU value was recorded as an individuals’ day-of-resting value and used to describe the change in blood pressure and heart rate over the eight weeks of training.

**Resting Cardiac Autonomic Measures:** Changes in resting HRV parameters were assessed over time. Time domain, frequency domain, and nonlinear measures of HRV were used to indirectly quantify cardiac autonomic modulation. The time domain measure selected was the standard deviation of normal R-R intervals (SDNN). Frequency domain measures included: total power, low-frequency power and normalized units of LF power (LFnu) as an assessment of sympathovagal modulation, high-frequency power and normalized unit of HF (HFnu) as an assessment of vagal modulation, and the ratio of low frequency power to high frequency power (LF/HF). Finally, nonlinear measures of HRV included Sample Entropy, a measure of predictability or complexity related to the degree of pattern repeatability with a time series where values close to zero represent high predictability and values close to 2 represent unpredictable or complex time series (Richman & Moorman, 2000). Continuous HR data for subsequent HRV analysis was initially collected using the Sunnto watch system. Frequent connection problems and changes in software with this system led to the replacement of the Sunnto watch system with the Polar watch system at approximately two-thirds of the way through study enrolment. All HR data files were uploaded into Kubios HRV Analysis Software 2.0 for Windows (The Biomedical Signal and Medical Imaging Analysis Group, Department of Applied Physics, University of Kuopio, Finland). This software is distributed free of charge on request (http://venda.uku.fi/research/biosignal). For each of the experimental visits the epoc window of interest was the final five minutes of seated rest.

**Cardiovascular Responses During Exercise:** Using continuous beat-to-beat data from the Finometer MIDI photoplethysmograph, the instantaneous cardiovascular (SBP, DBP, and HR) responses during the bout of MINT handgrip exercise were calculated as the change from resting Finometer values. Resting Finometer values for SBP, DBP, and HR were determined as the average of the remaining 8 per-minute values after omitting highest and lowest values. During each of the experimental exercise conditions beat-to-beat raw data was converted into 5sec averages and expressed as a change score from the aforementioned day-of-rest. Cardiovascular responses during MINT handgrip exercise were quantified using two calculation strategies; the average change score throughout the entire exercise duration and the maximum (peak) 5sec change score.
Arterial Augmentation Index and Pulse-wave Velocity: Participants rested in a supine position for 10min while being fitted for arterial assessments of radial augmentation index (AIx) and Carotid-Radial peripheral pulse wave velocity (PWV). AIx was determined by applanation tonometry of the right radial artery by using a pressure transducer and the SphygmoCor™ (Model-EM3, Atcor Medical, Sydney, Australia), Software Version 8.2. Carotid-radial pulse wave velocity (cPWV) was determined by sequential acquisition of pressure waveforms from the carotid and the radial arteries by use of the same tonometer. The radial and carotid pulses were located by palpation with the optimal tonometer location selected as the position that yielded the best quality signal output. The timing of these waveforms was compared with that of the R wave on a simultaneously recorded ECG. PWV was calculated as the difference in carotid to radial path length divided by the difference in R wave to waveform foot times. Path lengths were measured as a straight line from the suprasternal notch to the carotid and radial measurement sites, respectively. PWV and AIx as determined using the SphygmoCor™ system have been shown to be both reliable (Currie et al., 2009) and reproducible (Papaioannou et al., 2004). In-house reproducibility of AIx method by the primary investigator in a cohort of young mixed-sex individuals was previously reported (ICC: 0.90, p<0.01) (Bentley & Thomas, 2014). Unpublished work confirms high reproducibility by the primary investigator among older post-menopausal women for both AIx (ICC:0.9, p<0.01) and PWV (ICC: 0.56, p<0.05). For this research, a series of two measurements of AIx and PWV were taken sequentially on each side and then averaged for enhanced accuracy.

Exercise Performance and Perceived Exertion: During each experimental visit participants completed both (1) an assessment of maximum grip strength and (2) an assessment of handgrip performance while completing MINT exercise. To determine maximum grip strength three separate 5sec isometric holds were completed at maximal volitional contraction (MVC) with both the dominant and non-dominant hands. The greatest 1sec average force value was identified as maximum strength and used to bilaterally compare changes in strength over time. To determine handgrip performance while completing MINT exercise real-time force output was collected (ADInstruments, LabView software) throughout a bout of MINT exercise and used to quantify performance in two ways; an average performance score throughout the duration of exercise (expressed as both an absolute force value (kg) and a relative exercise intensity (% MVC)) and a time-dependent decline in grip performance during the MINT bout (expressed as a logarithmic equation derived from absolute force data). At the middle and at the end of the MINT exercise bout participants used the Borg Ratings of Perceived Exertion (RPE) scale (6-20) (Borg, 1982) to indicate exercise exertion. These scores were averaged together at each visit with a change in RPE over the eight weeks of training as the variable of interest.
**MINT Intervention:** The MINT exercise protocol is thirty-two separate 5sec intermittent handgrip contractions at maximal effort with 5sec rest in between repetitions. The protocol was designed to be both simple to understand and easy to execute, while accounting for some of the unique physiological responsiveness among older women (Chapter 4). Although prescribed as a maximal effort, previous research in our laboratory has demonstrated that the average relative exercise intensity of MINT is approximately 50% MVC (Chapter 4). While in the laboratory, participants complete the MINT protocol using an ADInstruments grip dynamometer with corresponding grip force analysis software (LabView). While completing at-home exercise training, the MINT protocol is completed with the MINT grip tool (Chapter 4).

**At-home Exercise Training:** The prescribed training intervention was 8 weeks of at-home handgrip exercise following the MINT exercise protocol (32x5sec, 5sec rest) against the MINT grip tool. Exercise was to be completed 4 times per week, separated by at least 24 hours and by no more than 72 hours. There were no restrictions on time of day or location. Participants were expected to self-monitor their own exercise protocol timing. All women were instructed not to change their diet and exercise levels. Exercise completion was recorded using a custom-designed online tracking system which allowed for the primary investigator to monitor exercise adherence throughout the entire training duration. All women received standard follow-up correspondence (email or telephone) at the 2-week and 6-week time points and completed experimental visits at the 0-week (Baseline), 4-week (Midway), and 8-week (End) time points.

**Statistical Analysis:** This research was primarily powered to detect changes in resting systolic blood pressure over time and used change in SBP values from a recent meta-analysis (Carlson et al., 2014). Extracting effect size information for the handgrip RCTs only reveals an average Cohen’s d of 1.4. Using an assigned α of 0.05, and β of 0.2, a minimum of eighteen participants was deemed sufficient to power intra-individual comparisons. Given that there were no associations between baseline values and corresponding training-induced change scores (p>0.05 for all), repeated measures analysis of variance (ANOVA) with Bonferroni post-hoc procedures were used to determine time dependent (0wks, 4wks, 8wks) changes in resting CV variables (SBP, DBP, HR). Repeated measures ANOVA with Bonferroni post-hoc procedures were also used to determine time dependent (0wks, 4wks, 8wks) changes in the instantaneous cardiovascular responses (SBP, DBP, HR), changes in HRV, and changes of handgrip performance data (absolute performance, relative performance (% of MVC)), and changes in ratings of perceived exertion during testing. Shapiro-Wilk tests were used to assess normality of HRV measures, with data undergoing logarithmic transformation as necessary. Two-way (time x arm) repeated measures
analysis of variance (ANOVA) with Bonferroni post-hoc procedures were used to explore changes in forearm strength, forearm girth, arterial augmentation index, and carotid-radial pulse wave velocity, over time (0wks, 4wks, 8wks) and between arms (trained and untrained). Pearson correlation coefficients were used to assess possible relationships between assessed measures. Statistical analyses were completed using IBM SPSS Statistics 22 (SPSS, Chicago, IL). All data is presented as Mean ± SD, unless specified otherwise. Statistical significance was set at p < 0.05. Exercise behaviour analysis was descriptive and includes exercise adherence percentages and PACES scores. Modified thematic analysis of the Questionnaire of Exercise Behaviours was completed according to the twelve common barriers to exercise in older adults (Neid & Franklin, 2002).

5.3 Results

Participants: Eighteen women began the training study. One woman withdrew due to an unrelated hand injury two weeks into the training. Therefore, a total of seventeen older (61.6 ± 4.0yrs, range: 57 to 68), women who were at least 1 full year post-menopausal (8.3 ± 4.5, range: 1.0 to 15.5yrs) completed eight weeks of at-home MINT handgrip training. Participants presented with various co-morbidities including pre-hypertension (n=7, two on BP medication), hypertension (n=4, two on BP medication), arthritis (n=4), eczema (n=1), hypothyroidism (n=1), Raynauds (n=1), diabetes (n=1), osteoporosis (n=1), asthma (n=2), arterial fibromuscular dysplasia (n=1), and palmer fibromatosis (n=1). From Baseline to End there was no change in weight, exercise behaviour (RAPA), or self-reported anxiety (State or Trait) (all p>0.05) (Table 5.1).

<table>
<thead>
<tr>
<th>Characteristic (MEAN ± SD)(n=17)</th>
<th>Baseline (day=0)</th>
<th>Midway (day=28±2)</th>
<th>End (day=56±4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.6 ± 4.0</td>
<td>61.6 ± 4.0</td>
<td>61.7 ± 4.0</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>158.1 ± 6.4</td>
<td>158.1 ± 6.4</td>
<td>158.1 ± 6.4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.4 ± 16.0</td>
<td>71.5 ± 15.9</td>
<td>71.5 ± 16.4</td>
</tr>
<tr>
<td>RAPA (score /10)</td>
<td>6.6 ± 2.4</td>
<td>6.8 ± 2.1</td>
<td>7.1 ± 2.5</td>
</tr>
<tr>
<td>Resting SBP (mmHg)</td>
<td>127.5 ± 13.6</td>
<td>121.7 ± 11.7*</td>
<td>122.4 ± 14.4*</td>
</tr>
<tr>
<td>Resting DBP (mmHg)</td>
<td>77.7 ± 8.1</td>
<td>75.7 ± 7.1</td>
<td>76.0 ± 8.7</td>
</tr>
<tr>
<td>Resting HR (bpm)</td>
<td>70.9 ± 8.3</td>
<td>67.3 ± 7.4*</td>
<td>69.7 ± 1.9</td>
</tr>
<tr>
<td>State Anxiety (score /80)</td>
<td>31.0 ± 7.4</td>
<td>30.3 ± 9.4</td>
<td>29.1 ± 7.8</td>
</tr>
<tr>
<td>Trait Anxiety (score/80)</td>
<td>31.9 ± 8.7</td>
<td>33.1 ± 8.0</td>
<td>32.5 ± 8.1</td>
</tr>
<tr>
<td>Medication Classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>n = 2</td>
<td>n = 2</td>
<td>n = 2</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>n = 1</td>
<td>n = 1</td>
<td>n = 1</td>
</tr>
<tr>
<td>Diuretic</td>
<td>n = 1</td>
<td>n = 1</td>
<td>n = 1</td>
</tr>
<tr>
<td>Antibiotic</td>
<td>n = 0</td>
<td>n = 0</td>
<td>n = 2</td>
</tr>
</tbody>
</table>

Table 5.1. Participant Characteristics Throughout the Training Study. * indicates difference from baseline, p<0.05.
Exercise Compliance and Self-Rated Effort: The majority of participants tracked their exercise behaviour using a custom-designed online tracking form. Alternatively, a subset of women (n=3) used a printed form. Based on self-reported exercise logs, adherence to the at-home training was high. Thirteen women completed all 32 training sessions, with the remaining four participants completing 31, 30, 27, and 25 sessions respectively. This equates to an average exercise adherence score of 96.9%. Furthermore, participants self-rated their at-home exercise effort consistently high (Scale of Exercise Effort (0-10)) throughout both the first half (8.5 ± 0.8) and second half (8.5 ± 1.0) of training.

Handgrip Performance Overtime: Grip performance measurements have been presented in Table 5.2. Grip strength displayed a significant interaction effect (p<0.05), with subsequent post-hoc comparisons indicating that 1sec maximum strength increased in the training arm only (+2.7 ± 2.4kg, p<0.05). This training effect provides evidence that the unilateral exercise prescription was followed. In addition to a training-induced effect on maximum grip force production, a progressive improvement in the average force production throughout acute MINT exercise bouts was observed(Midway: +1.8 ± 1.4kg, End: +2.6 ± 2.3kg, p<0.01). Absolute grip performance during the in-laboratory acute MINT exercise bouts improved, statistically demonstrated as the significant interaction effect between session (Baseline, Midway, End) x Grip Contraction (32 total) (p<0.05). Descriptively, this interaction can be best appreciated by comparing the average force output of the first five grip contractions (Baseline: 11.6 ± 3.8kg, Midway: 13.5 ± 4.3kg, End: 14.7 ± 4.5kg) to the average absolute force output of the final five grip contractions (Baseline: 7.9 ± 3.1kg, Midway: 10.0 ± 2.9kg, End: 10.2 ± 3.6kg). Due to the parallel improvement to both 1sec maximum strength and average grip performance, the average relative exercise intensity (%MVC) completed at each of the in-laboratory visits was not statistically significant. Furthermore, throughout the eights weeks of training there was no difference in participants’ in-laboratory ratings of perceived exertion (Baseline: 13.6 ± 1.7, Midway: 14.7 ± 2.6, End: 14.1 ± 2.2).

<table>
<thead>
<tr>
<th></th>
<th>1sec Maximum Grip Force</th>
<th>MINT Protocol Grip Performance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-dominant (kg)</td>
<td>Dominant (kg)</td>
</tr>
<tr>
<td>Baseline</td>
<td>18.6 ± 4.9</td>
<td>18.7 ± 3.3</td>
</tr>
<tr>
<td>Midway</td>
<td>20.6 ± 4.9*</td>
<td>19.5 ± 4.3</td>
</tr>
<tr>
<td>End</td>
<td>21.4 ± 5.0**</td>
<td>19.6 ± 3.8</td>
</tr>
</tbody>
</table>

Table 5.2. Grip Force Measures over Time. Significantly different from baseline * p<0.05, **p<0.01. Data presented are MEAN ± SD.
Participants used the same Scale of Exercise Effort (0-10) to self-report their in-lab exercise effort. There was no difference between the average self-rated effort during the laboratory visits (Baseline: 8.6 ± 1.0, Midway: 8.9 ± 1.1, End: 8.8 ± 1.2) as compared to the average at-home effort during both the first half (8.5 ± 0.8) and second half (8.6 ± 1.0) of training. This indicates consistency in exercise effort during the at-home, unsupervised training sessions.

**Blood Pressure and Heart Rate:**

Resting: There was a significant impact of the 8week MINT training program on resting SBP (F(1,32) = 5.57, p<0.01) with reductions at both the Midway (-5.9 ± 7.7mmHg, p<0.05) and the End (-5.1 ± 7.7mmHg, p<0.05) of training (Figure 5.2). In comparison, there was an insignificant effect of MINT on resting DBP (F(1,32) = 1.65, p>0.05). Heart rate was significantly reduced at the Midway point (-3.7 ± 5.3bpm, p<0.05) only.

Instantaneous Cardiovascular Response to HG Exercise: At each of the three experimental visits, MINT handgrip exercise caused elevations to average systolic BP (p<0.01 for all) and diastolic BP (p<0.01 at Midway and End). There was an insignificant heart rate response to the MINT exercise protocol at all experimental visits. Peak BP responses, identified within each participant as the maximum 5sec changes, remained below recently reported safety guidelines (<250/<115mmHg) at each visit for both systolic BP (Baseline: 171.5 ± 23.6mmHg, Midway: 175.8 ± 16.3mmHg, End: 181.3 ± 17.7mmHg) and diastolic BP (Baseline: 94.3 ± 14.1mmHg, Midway: 98.9 ± 14.7mmHg, End: 100.6 ± 11.9mmHg).
Table 5.3. The Training-dependent Cardiovascular Responses During a Bout of MINT Handgrip Exercise. Significant difference from day-of resting value, *p < 0.01. Significant difference from Baseline (Day 0), *p<0.05, **p<0.01. Data are presented as MEAN ± SD.

<table>
<thead>
<tr>
<th></th>
<th>Average Acute Change From Day-of Rest</th>
<th>Absolute Average Exercise Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Midway</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>26.8 ± 19.7*</td>
<td>35.5 ± 16.11*</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>5.8 ± 11.9</td>
<td>11.8 ± 11.2*</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>-1.5 ± 5.2</td>
<td>2.2 ± 5.3*</td>
</tr>
</tbody>
</table>

Figure 5.2 The Training Impact of MINT Handgrip Exercise on Resting Blood Pressure and Heart Rate. Results are presented as MEAN ± SEM. *p<0.05, as compared to Baseline.

Heart Rate Variability: Throughout the duration of this research study there were substantial technical problems with the Sunnto HR system and the switch to the Polar HR system occurred approximately halfway through baseline measurements. As a direct result of the Suunto system issues eight women were missing resting HRV and were subsequently removed from the time-dependent statistical analyses. Heart rate variability analyses were conducted on the remaining nine women. As indicated by significant
deviations to normality, logarithmic transformations were completed on the ratio values, LF (ms²) values, and HF (ms²) prior to statistical analysis. MINT handgrip training significantly reduced high frequency (normalized units) at the midway point only (4 weeks) (-3.6 ± 16.8, p<0.05). MINT training did not significantly change any other frequency or time-domain measure of HRV (p>0.05). There was also a significant effect of time for sample entropy (p<0.05), with heart rate complexity significantly increased by the 8week time (+0.24 ± 0.31, p<0.05)(Table 5.4).

Table 5.4. Time-domain (SDNN, RMSSD), Frequency-domain (LF, HF, ratio), and Non-linear (Sample Entropy) Results of Resting Heart Rate Variability over Time. *Significant difference compared to Baseline (0 weeks), p<0.05. Values are presented as Mean ± SEM.

<table>
<thead>
<tr>
<th></th>
<th>0 weeks</th>
<th>4 weeks</th>
<th>8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDNN</td>
<td>27.3 ± 4.5</td>
<td>31.1 ± 5.3</td>
<td>32.3 ± 4.9</td>
</tr>
<tr>
<td>RMSSD (ms)</td>
<td>16.5 ± 3.3</td>
<td>20.7 ± 4.5</td>
<td>20.9 ± 3.5</td>
</tr>
<tr>
<td>LF (ms²)</td>
<td>250.9 ± 77.9</td>
<td>785.0 ± 423.6</td>
<td>291.5 ± 92.2</td>
</tr>
<tr>
<td>HF (ms²)</td>
<td>126.3 ± 41.3</td>
<td>186.3 ± 77.8</td>
<td>177.8 ± 63.7</td>
</tr>
<tr>
<td>LF (nu)</td>
<td>65.0 ± 7.0</td>
<td>68.6 ± 4.8</td>
<td>62.3 ± 4.7</td>
</tr>
<tr>
<td>HF (nu)</td>
<td>35.0 ± 7.0</td>
<td>31.3 ± 4.8*</td>
<td>37.7 ± 4.7</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>3.5 ± 1.4</td>
<td>3.1 ± 0.9</td>
<td>1.8 ± 0.4</td>
</tr>
<tr>
<td>Sample Entropy</td>
<td>1.36 ± 0.10</td>
<td>1.47 ± 0.08</td>
<td>1.62 ± 0.11*</td>
</tr>
</tbody>
</table>

Augmentation Index and Pulse Wave Velocity. Forearm characteristics were similar between the dominant and non-dominant arms at Baseline, with no significant differences in girth, AIx, or crPWV. There were no changes to vascular structure as a result of MINT training, assessed as radial augmentation index and carotid-radial pulse-wave velocity (p>0.05 for all, Table 5.5).

Table 5.5. Bilateral Forearm Comparisons of Pulse Wave Velocity and Augmentation Index over Eight Weeks of Non-dominant Handgrip Training. Results are presented as Mean ± SD. AIx, augmentation index; PWV, pulse wave velocity (m sec⁻¹).

<table>
<thead>
<tr>
<th></th>
<th>0 weeks</th>
<th>4 weeks</th>
<th>8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominant Arm (non-training)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forearm Girth (cm)</td>
<td>24.7 ± 2.5</td>
<td>24.7 ± 2.8</td>
<td>24.9 ± 2.7</td>
</tr>
<tr>
<td>Radial AIx (%)</td>
<td>33.7 ± 5.9</td>
<td>34.9 ± 6.6</td>
<td>33.0 ± 6.9</td>
</tr>
<tr>
<td>Carotid-Radial PWV</td>
<td>7.3 ± 0.6</td>
<td>7.2 ± 0.8</td>
<td>7.2 ± 0.6</td>
</tr>
<tr>
<td>Non-Dominant Arm (training)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forearm Girth (cm)</td>
<td>24.6 ± 2.8</td>
<td>24.8 ± 2.7</td>
<td>24.8 ± 2.5</td>
</tr>
<tr>
<td>Radial AIx (%)</td>
<td>32.4 ± 6.2</td>
<td>35.0 ± 6.3</td>
<td>33.1 ± 6.6</td>
</tr>
<tr>
<td>Carotid-Radial PWV</td>
<td>7.2 ± 0.7</td>
<td>7.0 ± 1.0</td>
<td>7.2 ± 1.0</td>
</tr>
</tbody>
</table>

Exercise Barriers and Facilitators: Of the twelve previously published common barriers to exercise in older adults, five were identified by the current group of exercise participants at either Baseline (anticipated exercise barriers) or End (actual exercise barriers). The vast majority of anticipated barriers were in reference to Habit, specifically to the required time necessary to complete the MINT handgrip exercise. By the end of the eight week training program, Habit (specifically time) was still the most
commonly cited barrier. Those who identified the barrier of “Habit” reported a lower overall exercise adherence (94.1%) than those who did not (100%) with the difference approaching statistical significance (p=0.06). In addition, the barrier of Attitude was identified at the end of exercise completion with two women identifying displeasure towards how repetitive MINT exercise was (n=1) and how sedentary it was (n=1). All other reported anticipated/actual barriers remained quite low.

<table>
<thead>
<tr>
<th>Common Barriers</th>
<th>Anticipated Exercise Barrier Baseline (day=0)</th>
<th>Actual Exercise Barrier End (day=56±4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None Reported</td>
<td>35.3% (n=6)</td>
<td>29.4% (n=5)</td>
</tr>
<tr>
<td>Self-efficacy</td>
<td>11.8% (n=2)</td>
<td>5.9% (n=1)</td>
</tr>
<tr>
<td>Attitude</td>
<td>-</td>
<td>11.8% (n=2)</td>
</tr>
<tr>
<td>Injury</td>
<td>5.9% (n=1)</td>
<td>-</td>
</tr>
<tr>
<td>Habit, specifically Time</td>
<td>47.1% (n=8), 23.6% (n=4)</td>
<td>52.9% (n=9), 17.7% (n=3)</td>
</tr>
<tr>
<td>Cognitive Decline</td>
<td>11.8% (n=2)</td>
<td>5.9% (n=1)</td>
</tr>
</tbody>
</table>

Table 5.6. Thematic Matching of Perceived and Actual Barriers to MINT Handgrip Exercise.

5.4 Discussion

At a time where non-pharmaceutical treatment options are desired by both clinicians and patients, research dedicated towards exploring at-home exercise options is strengthened when both assessments of exercise efficacy and exercise effectiveness are completed. This research has identified that eight weeks of high intensity interval handgrip exercise can effectively reduce resting systolic blood pressure (127.5 ± 13.6mmHg to 122.4 ± 14.4mmHg, p<0.05) and improve heart rate complexity (1.36 ± 0.10 to 1.62 ± 0.11, p<0.05) in a cohort of older post-menopausal women with a range of resting blood pressure and various comorbidities. In addition to this noted exercise efficacy, program adherence was high for this at-home handgrip training (96.9%) with participants indicting high levels of exercise enjoyment (PACES: 91.9 ± 13.2).

Handgrip Training Response: MINT handgrip training provided a significant training stimulus for at-home use. This is evident by both the improvement in non-dominant maximal grip strength and the improvement in absolute grip performance throughout the duration of an acute MINT exercise bout. In line with the augmented grip force performance, representing an enhanced underlying central command drive, the instantaneous changes to BP and HR also experienced a significant training response with the average systolic BP response increasing as compared to Baseline (Mid: 8.7 ± 19.16mmHg, End: 15.7 ± 15.9mmHg). Similar training effects were evident for diastolic BP (Mid: 6.0 ± 15.5mmHg, End: 8.7 ± 11.4mmHg) and heart rate (Mid: 3.7 ± 4.1bpm, End: 4.3 ± 4.1bpm). Despite the enhanced cardiovascular drive, this pilot research demonstrates that 5sec peak exercising BP values remain similar throughout the
eight weeks of training. The clinical relevance of these findings remains to be fully elucidated. Future research which employs longer training program durations would be able to determine if there is ceiling effect to the both improvements in strength and enhanced cardiovascular drive.

**Blood Pressure Training Response:** This research supports and extends with a new training strategy, the consensus that handgrip exercise training reduces resting blood pressure. In recognition of the seemingly robust training response, the American Medical Association scientific statement of alternative approaches to help lower BP has identified isometric handgrip exercise (Class IIB, Level of Evidence C) as a reasonable modality for individuals with BP levels exceeding that of SBP/DBP: 120/80mmHg (Brook et al., 2013). Our current experimental reduction is slightly lower than recent meta-analyses (MEAN [95%CI]) (-6.8mmHg [-7.9 to -5.6]). However, with large effect sizes of SBP comparisons (Baseline to Midway: $r = 0.61$, Cohen’s $d = 1.54$, Baseline to End: $r = 0.56$, Cohen’s $d = 1.35$) we are confident in our overall training effect, with twelve research participants (70.6%) experiencing clinically relevant SBP reductions of greater than 2 mmHg (Pescatello et al., 2004).

**Mediators of the Blood Pressure Response:** This study assessed arterial structure and heart rate variability as potential mediators of the blood pressure training response to MINT exercise. Arterial structure was determined using the non-invasive measurements of crPWV and AIx and intra-individual comparisons were completed using the trained versus untrained arms. Although previous research with young men has documented that whole-body (Yoon et al., 2010) and upper-limb (Fahs, Heffernon, & Fernhall, 2009) resistance training undesirably increases augmentation index, this effect is not replicated among older women completing whole-body resistance training (Kingsley & Figueroa, 2012). Our research shows that augmentation index is also not altered following eight weeks of high intensity handgrip exercise. This finding provides additional support in favour of at-home handgrip training for older women.

Measurements of heart rate variability created considerable technical challenges. A poor connection between the Suunto chest strap and the wrist watch resulted in missing data during portions of each visit. The impact of the poor connection issues went undetected for a period of time while a Sunnto software update blocked the transfer of files for Kubois HRV analysis. After navigating the file transfer roadblock and uploading backlogged HRV files, the poor connection was retroactively detected. Common technical issues with heart rate strap use include strap placement location, sensor-to-skin connectivity, and subcutaneous fat content. Throughout the duration of the experimental visit great lengths were taken to avoid these connection issues, including posture reminders, tightening and relocating the heart rate strap,
and the use of Tensive (conductive adhesive gel) for enhanced connectivity on the chest sensors. Ultimately, the decision was made to switch from the Sunnto heart rate system to the Polar system. Strap connection issues were immediately rectified and all collected data after this point was clean and usable for data analysis. Unfortunately, due to missing baseline measures only nine of our seventeen women were included for HRV analysis.

Despite the noted loss in sample size, this research was still able to demonstrate that high intensity handgrip exercise can significantly enhance HR complexity (ie. sample entropy) among older women. Increased sample entropy suggests that the HR signal became more complex and less predictable (Goldberger et al., 2000). Previous research has suggested that sample entropy may be a marker of dynamic sympathovagal interactions (Porta et al., 2007). Thus, the changes in nonlinear HRV measures support the finding by Millar et al. which suggest handgrip exercise can improve cardiac vagal modulation (2013). Furthermore, this research is in support of the use of non-linear indices of HRV for the detection of subtle, yet important, modulations in HR behaviour (Makikallio, Tapanainen, Pulppo, & Huikuri, 2002). A potential explanation for why this research was able to detect a statistically significant change in heart rate complexity with such a limited sample size was the strong methodology in controlling for external factors that can influence HRV. This research controlled for day of time, food ingestion, alcohol use, medication use, and bladder/gastric distension, as recommended (Quintana & Heathers, 2014).

**Safety:** Isometric exercise has been described classically as inducing a pressure load on the heart based on its potential to increase both systolic and diastolic BP (Millar et al., 2014). The most recent clinical exercise guidelines have identified problematic peak exercise values of >250mmHg for systolic BP and >115mmHg for diastolic (American College of Sports Medicine, 2013). The research is in support of others who have observed the acute cardiovascular responses to handgrip exercise fall far below these identified exercise limits (Chapter 3, Araujo et al., 2011). Among older women specifically, our research group has previously identified that in a cohort of normotensive, otherwise healthy, post-menopausal women neither sustained moderate intensity handgrip exercise (SBP: 145.0 ± 20.3mmHg; DBP: 89.6 ± 9.3mmHg) nor high intensity interval handgrip exercise (SBP: 150.3 ± 20.1mmHg; DBP: 89.6 ± 9.5mmHg) resulted in concerning peak blood pressure values. In addition, the current results of peak cardiovascular responses among a heterogeneous cohort of older women with various co-morbidities, including pre-hypertension (n=7) and hypertension (n=4), provide additional evidence that high intensity handgrip exercise does not produce cardiovascular responses which pose a risk. Finally, there were no research participants who experienced any musculoskeletal injuries during the handgrip exercise. This
information will be useful to future researchers wishing to employ at-home, unsupervised exercise training options.

**Study Limitations and Conclusions:** This study was designed as a prospective cohort study with intra-individual controlled comparisons of trained vs. untrained arms. As a result, there was no designated control group, which increases the probability for type I error. As we move forward with future evaluations of the MINT handgrip exercise strategy, long-term assessments which include an active sham-training control will be employed. Although it was impossible to methodically blind research participants to the intervention design, we attempted to control expectation-driven experimental error by telling participants that the primary research variables of interest were the vascular assessments of augmentation index and pulse wave velocity. Furthermore, all assessments of blood pressure, heart rate, augmentation index, and pulse wave velocity were completed by standardized in-laboratory medical devices that do not involve operator interpretation. As such, the influence of experimenter bias was considered negligible.

In conclusion, this proof of concept research study was able to successful demonstrate both exercise efficacy and exercise effectiveness in reference to the Maximal INTerval (MINT) handgrip exercise strategy, consisting of 32x5sec maximal grip squeezes separate by 5sec of rest against an in-house grip tool. Eight weeks of at-home exercise training with this simple, easy, and highly accessible handgrip exercise option successfully reduces resting systolic pressure and increases heart rate complexity among a highly variable group of post-menopausal women.
6.1 Introduction

Recent primary and systematic review literature supports the use of handgrip (HG) exercise training of at least four weeks as a means of successfully reducing resting blood pressure (BP) with substantive meta-analytic data (Mean Difference, 95% CI) supporting reductions in systolic BP (-6.88, -8.31 to -5.46 mmHg), diastolic BP (-3.64, -4.69 to -2.58 mmHg), mean arterial pressure (-3.65, -4.90 to -2.40 mmHg) and heart rate (-0.76, -1.19 to -0.32 bpm) (Inder et al., 2015). Significant training effects have been reported in older cohorts with normotension (Millar et al., 2008) in addition to those with above-optimal resting blood pressures (Badrov et al.; 2013; Kumar et al., 2010; McGowan et al., 2007; Millar et al., 2013). While the evidence suggests a robust training response, evaluation of individual research reports indicates that HG training adaptations demonstrate a high degree of inter-individual variability.

One way to further examine the interindividual differences observed with HG training is to assess cardiovascular reactivity responses to psychological stressors (Badrov et al., 2013b; Millar, Bray, MacDonald, & McCartnery, 2009a). Cardiovascular (CV) reactivity refers to the acute CV responses of BP and heart rate (HR) during situations of physical or mental stress, such as cold pressor, public speaking, mental arithmetic and isometric exercise. The reactivity hypothesis explains that large BP and HR reactions to stressors are linked to cardiovascular pathology (Lovallo & Gerin, 2003; Schwartz et al., 2003) and correlated to future development of hypertension and CV disease (Allen, Matthews, & Sherman, 1997; Carroll, Phillips, Der, Hunt, & Benzeval, 2011; Flaa, Eide, Kjeldsen, & Rostrup, 2008; Matthews et al., 2004). The difference between cardiovascular perturbations to psychological stress and the cardiovascular perturbations to exercise is that the latter is metabolically appropriate, whereas the former is not (Balanos et al., 2010; Orbist, 1981). Attenuations in CV reactivity to psychophysiological stressors may be one mechanism by which exercise training lowers CV disease related morbidity and mortality (Blumenthal et al., 1990).

A retrospective study of the relationship between psychophysiological CV reactivity and handgrip exercise with healthy older participants reported that an individual’s CV reactivity to a serial subtraction
stressor was highly correlated to reductions in SBP resulting from eight weeks of HG training (Millar et al. 2009a). The correlation between training-induced BP reductions and psychophysiological CV reactivity was confirmed using a prospective research design among older hypertensives, with high correlations demonstrated between SBP reductions and SBP reactivity to both a serial subtraction stressor ($r = -0.85$) and an acute handgrip stressor ($r = -0.079$) (Badrov et al. 2013b). This research also demonstrated that ten weeks of HG training attenuated SBP reactivity to both serial subtraction (-7mmHg) and handgrip (-8mmHg) stressors (Badrov et al. 2013b).

Both Millar et al. (2009a) and Badrov (2013b) utilized the same moderate intensity HG design for their exercise training interventions; 4 x 2min sustained contractions @ 30%MVC with 1min rest between sets. High intensity intermittent grip training also reduces resting BP among both older women and older normotensive men and women (Kumar et al., 2010)(Chapter 5). In comparing the acute physiological responses to these two HG exercise designs, our lab has speculated that the autonomic nervous system may elicit dissimilar patterns of reactivity, with moderate intensity sustained HG exercise potentially driving CV responses through the metaboreflex and high intensity intermittent handgrip driving CV responses through the mechanoreflex (Chapter 3). An assessment of the relationship between CV reactivity to psychophysiological stressors and training-induced responses to a high intensity intermittent HG training intervention has yet to be examined.

This study explores the relationship between cardiovascular reactivity to psychophysiological stressors and HG training-induced effects brought on by high-intensity intermittent HG exercise training. The purpose of this study was to prospectively investigate whether: (a) cardiovascular stress reactivity responses to psychophysiological stressors are predictive of HG-induced training responses, and (b) high intensity intermittent handgrip training attenuates CV reactivity to psychophysiological stressors. We utilized the serial subtraction task (SST) and HG task (HGT) to explore these potential relationships. Based on previous research showing improved central autonomic function follow HG training (Badrov et al., 2013b; Millar et al., 2009a; Taylor et al., 2003) it was hypothesized that: (a) cardiovascular reactivity to the centrally mediated SST and HGT would be predictive of HG-induced training reductions in resting BP, and (b) cardiovascular reactivity to SST and HGT would be attenuated following HG-training.

6.2 Methods

This study was approved by the Research Ethics Board at the University of Toronto (REB#31450) and is accordance with the guidelines set forth by the Declaration of Helsinki (World Medical Association,
2013). All participants provided written informed consent after receiving a full explanation of all experimental procedures, exercise protocols, and possible risks associated with participation in the study.

**Participants:** Participants were recruited from the greater Toronto area using online and word-of-mouth communication strategies. Inclusion criteria were kept broad for enhanced applicability and included: post-menopausal (≥ one year since last menstrual bleed), without current/previous use of hormone therapy medication, resting systolic blood pressure >115mmHg. Exclusion criteria were: current or previous diagnosed cardiovascular disease (aside from hypertension), current smokers, otherwise unable to participate in handgrip exercise (ie. hand injury).

**Study Design:** This study was a prospective exploration of CV reactivity and HG training-induced effects brought on by eight weeks of training using a high-intensity intermittent HG exercise design. Prior to any experimental acquisition of data participants were initially habituated to the lab, the experimenter, the exercise protocols, and the equipment. Participants completed mock laboratory procedures where data was recorded but not analyzed. Three experimental visits were: pre-training (day=0), midway (day = 28 ± 2 days), and post-training (day = 56 ± 4 days). Experimental visits were for detailed physiological assessments, the results of which have been previously described (Chapter 5). Exploration of the relationship between cardiovascular reactivity and HG training effects utilizes unpublished data from the pre-training (day= 0) and post-training (day=56) experimental visits.

**Handgrip Exercise Training:** All participants trained at-home 4 days/week for eight weeks. Prescribed handgrip training (MINT: Maximum INTensity handgrip (Chapter 4) was a high intensity intermittent design and consisted of 32 x 5sec contractions at maximal perceived force with 5sec rest in between sets. At home exercise was completed using a custom made handgrip tool. The acute and post-exercise physiological responses to this specific HG protocol have previously been determined to be safe and tolerable (Chapter 3) and the at home-tool has been specifically designed according to the preferences of older women (Chapter 4). During their pre-exercise laboratory visit participants were provided detailed written instructions on how to complete the HG exercise to ensure proper at-home training. To measure exercise adherence, participants completed online tracking forms where they recorded the date and location of exercise completion as well as self-rated their exercise effort. To assess the possible impact of confounding factors throughout the eight weeks of training we monitored physical activity levels (Rapid Assessment of Physical Activity questionnaire)(Topolski et al., 2006), weight, medication use, and level of anxiety (State-Trait Anxiety Inventory (STAI) (Spielberger, et al., 1983).
**Experimental Protocol:** All testing was performed in an isolated room (free from external noise and distractions) within the Human Health and Performance Laboratory at the University of Toronto between the hours of 2:00-8:00pm to reduce the impact of diurnal variations in blood pressure (Jones et al., 2010). To control for external perturbations to BP, prior to each experimental visit participants completed a 4hr fast, 4hr abstinence from caffeine, and a 24 hr abstinence from both alcohol and strenuous activity. Upon arrival at the lab participants completed relevant questionnaires (RAPA, compliance quiz, STAI) and transitioned to a seated position for assessments of resting BP, resting HR, and CV reactivity to both a handgrip stressor (HGT) and a serial subtraction mental arithmetic test (SST). An automated oscillometric brachial cuff (BpTRU Vital Signs made by Medical Devices, model #BPM-100, BC Canada) was positioned on the left arm for discontinuous BP and HR recordings during rest. The right arm was supported at heart level and fitted with a photoplethysmographic finger cuff (Finometer MIDI made by Finapres Medical Systems, model#2, Arnhiem Netherlands) on the middle phalanx of the right third digit for beat-to-beat recordings of BP and HR during the resting time and during each of the reactivity stressors. The timing sequence of seated rest progressed as: 5mins rest (no data collection), 10mins of day-of resting data collection (BpTRU and Finometer), first CV reactivity stressor (Finometer), 5mins rest (Finometer left running, no analysis of data), second CV reactivity stressor (Finometer). The order of CV reactivity stressors was randomly determined and participants were blind as which stressor they would be completing first until it was presented.

**Resting Blood Pressure and Heart Rate:** Resting BP and HR were determined during the 10min resting time point by the BpTRU device which recorded a reading once every two minutes for a total of six recordings. The highest and lowest values were dropped and the remaining 4 values averaged. Change in resting BP and HR as a result of the eight weeks of HG training was calculated by subtracting (post-exercise) – (pre-exercise) values.

**Cardiovascular Reactivity (general):** During the resting time, beat-to-beat values of SBP, DBP and HR were also acquired using the Finometer and calculated into per minute averages (11 total recordings). The highest and lowest values were dropped and the remaining nine recordings averaged. During each of the psychophysiological stressors beat-to-beat responses of the CV system were collected and partitioned into 30 second segments. Cardiovascular reactivity was determined as the largest 30sec deviation from day-of rest. Statistical analyses were completed using calculated CV change scores, as recommended (Llabre, Spitzer, Saab, Ironson, & Schneiderman, 1991).

**Serial Subtraction Stressor:** Participants were presented a sequence of 25 four-digit numbers on a laptop screen. Each number was displayed for 5sec before automatically transferring to the next number. Participants were instructed to mentally subtract a two digit number and say the answer aloud. At pre-testing, all participants were told to subtract the number 17. At post-testing participants were presented
with a different sequence of 25 numbers, and randomly told to subtract either 17 (n=14) or 13 (n=3). The numbers 17 and 13 have both been previously used to successfully elicit CV responses (Badrov et al., 2013b; Millar et al., 2009a).

**Isometric Handgrip Tasks:** For the handgrip task (HGT) participants completed a single 2min isometric contraction at 30% of the participant’s day-of maximum grip strength, using their non-dominant hand (left for all) on a programmed handgrip dynamometer (ZonaPLUS: Zona Health, Boise, ID.). Participants’ compliance scores, automatically calculated by the device as the time a participant maintains the 30% MVC, were all ≥ 93%. The HGT protocol was identical at pre- and post-exercise experimental visits.

**Statistical Analysis:** This research was powered to detect changes in CV reactivity over time and used change in SBP values for sample size calculation. In an older, mixed-sex sample of pre-hypertensives completing 10 weeks of handgrip exercise, SBP reactivity to SST was reduced from 23±12 to 16±18 and SBP reactivity to IHGT was reduced from 26±12 to 18±8 ((estimated effect sizes of at least: 0.47) (Badrov et al., 2013b)). Using the effect size of r=0.47 (Cohen’s d = 1.07), an assigned α of 0.05, and β of 0.2, fifteen participants was deemed sufficient to power intra-individual comparisons. Changes in resting SBP, DBP, and HR following the at-home training intervention were obtained from the data file from (Chapter 5). For the purpose of this manuscript the impact of the HG training intervention in altering resting SBP, DBP, and HR was determined using dependent t-tests. Dependent t-tests were used to determine if absolute CV reactivity scores differed from day-of resting, if there was a difference in reactivity change scores between SST and HGT stressors, and if there was a training-induced augmentation to CV reactivity. The relationship between CV reactivity and HG-induced BP reductions was assessed using Pearson correlation coefficients between the cardiovascular reactivity values and the residualized HG systolic BP change score. Residualized change scores were used because pre-intervention resting BP has been previously shown to be highly correlated with the magnitude of BP reductions in HG-interventions (Millar, Bray, McGowan, MacDonald, & McCartney, 2007). Residualized change scores were obtained by regressing pre to post-change scores on pre-exercise values (Cohen, Cohen, West, & Aiken, 2004). Statistical significance was set at p < 0.05

### 6.3 Results

**Participants:** Eighteen women began the training study. One woman had to withdraw due to an unrelated hand injury. Therefore, a total of seventeen women completed eight weeks of high intensity HG training, with participant characteristics fully described in Chapter 5 (Table 5.1). Based on self-reported
exercise logs, adherence to the at-home training was very high at both the 4-week follow-up (100%) and the 8-week follow-ups (96%). Furthermore, participants self-rated their at-home effort consistently high (Scale of Exercise Effort (0-10)) throughout both the first half (8.5 ± 0.8) and second half (8.6 ± 1.0) of training. There were no reported changes in physical activity levels, diet, or anxiety levels.

**Handgrip Training Effects:** Following eight weeks of unilateral high intensity HG training there was a significant reduction in systolic BP (-5.1 ± 7.7mmHg (p<0.05), r = 0.56, Cohen’s d = 1.35), with 70.6% of participants experiencing a clinically relevant reduction of ≥ 2 mmHg (Pescatello et al., 2004). In comparison, there were statistically insignificant reductions in diastolic BP (-1.7 ± 5.2mmHg, p = 0.19) and HR (-1.2 ± 4.8bpm, p = 0.32).

**Effects of Handgrip Training on Cardiovascular Reactivity:** At pre-training, SST caused significant elevations in systolic BP, diastolic BP, and HR (all p<0.01), whereas HGT significantly elevated systolic BP and diastolic BP only (both p<0.01)(Table 6.2). An individual’s systolic BP responses to the two stressors were not correlated (r = 0.29, p = 0.26). Cardiovascular reactivity to SST and HGT changed as a result of handgrip training. The systolic BP reactivity response revealed a significant interaction effect between time (pre-training to post-training) and stressor (SST vs HGT) (p<0.05) with the SBP response to SST decreasing as a result of HG training (-2.7 ± 13.1mmHg) and the SBP response to HGT increasing as a result of HG training (5.3 ± 13.3mmHg) (Table 6.1, Figure 6.2). A similar trend of diastolic BP reactivity to the two stressors was observed, with the DBP response to SST insignificantly decreasing as a result of HG training (-2.3 ± 5.3mmHg) and the DBP response to HGT insignificantly increasing (0.6 ± 5.4mmHg) (interaction effect, p = 0.09). There was no effect of HG training on the HR reactivity response. CV reactivity was not related to age or to day-of indices of anxiety assessed through State or Trait anxiety scores (all p>0.05).

<table>
<thead>
<tr>
<th></th>
<th>Pre-training</th>
<th>Post-training</th>
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<tbody>
<tr>
<td><strong>Serial subtraction task</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔSBP (mmHg)</td>
<td>21.7 ± 20.5 *</td>
<td>19.0 ± 13.8 **</td>
</tr>
<tr>
<td>ΔDBP (mmHg)</td>
<td>10.2 ± 7.0 *</td>
<td>7.9 ± 5.0 *</td>
</tr>
<tr>
<td>ΔHR (bpm)</td>
<td>5.4 ± 5.9 *</td>
<td>5.4 ± 6.4 *</td>
</tr>
<tr>
<td><strong>Isometric Handgrip Task</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔSBP (mmHg)</td>
<td>10.9 ± 12.9 **#</td>
<td>16.2 ± 7.7 *</td>
</tr>
<tr>
<td>ΔDBP (mmHg)</td>
<td>5.7 ± 5.5 * #</td>
<td>6.4 ± 3.5 *</td>
</tr>
<tr>
<td>ΔHR (bpm)</td>
<td>1.2 ± 3.7 **#</td>
<td>1.2 ± 3.2 #</td>
</tr>
</tbody>
</table>

Table 6.1 Cardiovascular Reactivity Responses at Pre- and Post-training. Values are MEAN±SD. Significant difference compared to day-of resting, *p<0.01. Significant difference between stress tasks, #p<0.05, **p<0.01. Significant effect of training, *p<0.05.
Cardiovascular Reactivity to the Serial Subtraction Test and the Handgrip Test at Pre- (black bars) and Post-training (grey bars). Significant interaction effect between time (pre-exercise to post-exercise) and stressor (SST vs HGT) (*p<0.05) with the SBP responses the SST decreasing as a result of HG training and the SBP response to HG increasing as a result of HG training. Error bars are SEM.

Cardiovascular Reactivity as a Predictor of Isometric Handgrip Training Effectiveness: Pre-training diastolic BP reactivity to HGT (Figure 1) was significantly associated with IHG training-induced residualized reductions in systolic BP (p< 0.05). There were no other significant relationships. Baseline state and trait anxiety scores were not related to any of the cardiovascular reactivity responses to the SST or the HGT (all p>0.05).

6.4 Discussion

This prospective study was the first to investigate the relationship between SBP reductions brought on by a high intensity intermittent handgrip exercise program and measures of cardiovascular reactivity. Among a population of heterogeneous post-menopausal women with a wide range of resting blood pressures, an individual’s pre-exercise CV reactivity does not robustly predict their training-induced SBP reductions. Furthermore, there is a limited impact of high intensity HG exercise training on CV reactivity to psychophysiological stressors, with a reduced systolic BP reactivity to a serial subtraction stressor and an enhanced systolic BP reactivity to a handgrip stressor.
Figure 6.2 Correlation Analysis of Cardiovascular Reactivity to Serial Subtraction Test and Handgrip Test. 
(a) systolic blood pressure. (b) diastolic blood pressure. (c) heart rate.
In agreement with previous research, the SST and HGT stressors caused significant cardiovascular reactivity responses. Of the many possible CV reactivity stressors, we chose to include those with previously reported relationships to HG-induced reductions in resting BP. As such, two CV stressors were included in this research; the serial subtraction test (a psychological stressor) (Badrov et al., 2013b, Millar et al 2009a), and a 2-minute isometric handgrip contraction (a physiological stressor) (Badrov et al., 2013b). Although the cardiovascular responses to stressors are highly variable between individuals (Manuck 1994; Steptoe, 2008), within a person the reactivity response to an individual stressor is a relatively stable trait (Kamarck, Jennings, Pogue-Geile, & Manuck, 1994; Manuck, 1994).

**Effects of Isometric Handgrip Training on Cardiovascular Reactivity:** Both the HGT and the SST have been identified as primarily centrally mediated stressors, with distinct physiological and psychological underpinnings. Following eight weeks of HG training there were distinct responses of CV reactivity two these two stressors. Systolic BP reactivity to SST was reduced with training (-2.7 ± 13.1mmHg) while systolic BP reactivity to HGT was augmented (5.3 ± 13.3mmHg). Although statistically insignificant, a similar trend of diastolic BP reactivity to the two stressors was observed (SST: -2.3 ± 5.3 mmHg, HGT: 0.6 ± 5.4mmHg, p = 0.09). The significance of this dissimilar pattern of CV reactivity between stressors remains unclear; however evidence suggests that exaggerated physiological stress responses are associated with future risk of hypertension (Carroll et al., 2011, Flaa et al., 2008). The HG stressor task completed in this research was a submaximal static hold with the non-dominant hand (left for all) at a relative exercise intensity of 30% of the participant’s day-of maximum strength. The same relative intensity prescription was followed at both the pre-training and post-training experimental visits. However, eight weeks of MINT training increased participant’s non-dominant grip strength by 15% (2.8 kg). Although the same relative intensity was followed, the enhanced absolute workload of the HG stressor at the post-training visit may have provided a stronger stimulus to mechanoreceptors and therefore driven BP through the exercise pressor response. Intramuscular receptors respond to the peak tension developed by the working muscle (Hayward et al., 1991; Kaufman et al., 1983; Mense & Stahnke, 1983). Although others have reported attenuations in the SBP reactivity to HGT after a HG training program, unreported effects of training on grip strength results in the inability to distinguish the psychophysiological stress response from the exercise pressor response. Our findings suggest that in the context of an effective HG resistance training program the CV stressor of HGT may be an inappropriate test to provide comparable information regarding the CV reactivity of respondents. Future research examining CV reactivity throughout a HG training intervention can avoid this methodological issue in one of two ways; (1) consider alternative psychophysiological stressors such as serial subtraction, public
speaking, and timed reactivity tasks only or (2) use the un-trained arm in a unilateral training program during the reactivity response.

**Cardiovascular Reactivity as a Predictor of Isometric Handgrip Training Effectiveness:** The current results do not support previous work which reported CV reactivity as a useful means of potentially explaining the inter-individual variability in BP training response to HG exercise training (Badrov et al., 2013b; Millar et al., 2009a). This discrepancy can be examined by comparing the absolute CV reactivity scores between trials. Although similar psychophysiological stressors were used as laboratory assessments, there are noteworthy discrepancies in the absolute reactivity values responses. Miller et al. assessed an older (66 ± 8 yrs), otherwise healthy, normotensive (125/69 mmHg) men (n=10) and women (n=7) with resulting CV reactivity to SST that was higher than current results (SBP: +22 mmHg, DBP: +16 mmHg, HR: +19 bpm) (Millar et al. 2009). Similarly high CV reactivity values can be seen among an older (65 ± 7 yrs), medicated, hypertensive (129/72 mmHg) group of men (n=6) and women (n=6) with reactivity to both SST (SBP: +23 mmHg, DBP: +9 mmHg, HR: +9 bpm) and HGT (SBP: +26 mmHg, DBP: +11 mmHg, HR: +10 bpm). The discrepancy cannot be explained by stressor methodology (as the same reactivity methods were used), age (similar across all research reports), or participant resting blood pressure(similar across all research). A noteworthy difference between the research groups is the biological sex of the participants.

Strong meta-analytic data indicate that in response to psychological stress, such as mental arithmetic, men react with greater SBP, DBP and overall sympathetic reactivity (Brindle, Ginty, Phillips, & Carroll, 2014). Given that autonomic activity during acute psychological stress exposure involves both beta-adrenergic sympathetic activation and vagal withdrawal to roughly the same extent (Brindle et al., 2014), and age is known to attenuate beta-adrenergic sensitivity when comparing pre- to post-menopausal women (Lavi et al., 2007), the reduced CV reactivity to the SST stressor in the current study agrees with previous work showing sex differences in reactivity may be mediated by differential beta receptor sensitivity (Girdler, Hinderliter, & Light, 1993a). Furthermore, in comparison to their age-matched men, women have also been shown to present with blunted pressor reactions to exercise stressors such as resistive handgrip exercise (Dart et al., 2002). Although neither Millar et al (2009a) nor Badrov et al (2013b) statistically determined the impact of sex, both research groups recruited older mixed-sex samples in which the higher reactivity of men may have influenced the average reported values. Future research with the primary objective of determining the sex-dependent relationship between CV reactivity and resulting HG-exercise induced BP changes is necessary in order to further understand the autonomic nervous system’s role in BP reduction and how this role differs for men and women.
Sex-specific CV reactivity research would be especially impactful if responders were stratified based on their responder type patterns: myocardial, vascular, and mixed-mild patterns. When examining the variables responsible for driving BP modification, myocardial responders primarily drive BP through changes to cardiac output, whereas as vascular responders primarily drive BP through changes to total peripheral resistance (Brindle et al., 2014; Kline et al., 2002). In young cohorts, without controlling for menstrual phase, women are more likely to present as vascular or mixed-mild responders (Kline et al., 2002). Cyclic fluctuations of estrogen have been shown to impact the responder patterns, with high levels of circulating estrogens coupled to the luteal phase of the menstrual cycle associated with enhanced cardiac output reactivity and reduced vascular resistance reactivity (Girdler, Pederson, Stern, & Light, 1993b). As women transition through menopause and lose endogenous estrogens perhaps their pattern of CV reactivity changes in accordingly (Girdler et al., 1993a). Future research exploring these responder type patterns and the direct impact of the menopause transition is required to validate these speculative hypotheses.

**Conclusions and Future Directions:** In conclusion, this research was the first to investigate the impact of a high intensity internal HG training on measures of CV reactivity, demonstrating unique CV reactivity among older post-menopausal women. Pre-exercise CV reactivity to SST and HGT does not robustly predict training-induced SBP reductions. Furthermore, this research shows that high intensity HG exercise reduces systolic BP reactivity to a serial subtraction stressor. Together, this research provides further support and justification for sex-specific assessments of the autonomic responses among the aging population.
CHAPTER 7
Summary, Limitations, and Conclusions

7.1 Summary

The hypotheses tested in this dissertation provided a framework for the overall design and evaluation of a novel handgrip exercise strategy. This strategy, termed the Maximal INTerval handgrip strategy (MINT) included both a high intensity intermittent exercise protocol and a participant-informed grip tool. The four studies that formed the basis of this thesis are summarized below.

The first study (Chapter 3) used a within-participants randomized design with a control session to examine the acute cardiovascular responses of post-menopausal women to handgrip exercise over two time windows: (1) the real-time responses of blood pressure and heart rate were examined during a unilateral bout of handgrip exercise, and (2) the post-exercise recovery of blood pressure and heart rate were examined for thirty minutes following exercise cessation. The real-time and post-exercise responses were quantified and compared between three experimental visits: a moderate intensity HG design with sustained isometric grip contractions, a high intensity HG design with intermittent maximal grip contractions, and a comparative inactive control experimental visit.

The first hypothesis stated: both exercise designs will instantaneously drive systolic and diastolic BP, with greater values associated with the high intensity design. Key Findings: In support of this hypothesis, both a high-intensity intermittent HG design and a moderate-intensity sustained HG design resulted in significant elevations of BP, with greater elevations during the high intensity design (p<0.05).

The second hypothesis stated: despite augmented instantaneous cardiovascular responses, high intensity handgrip exercise will promote a more rapid return of BP to day-of resting values. Key Findings: In support of this hypothesis, BP following high intensity exercise returned to day-of values while BP following moderate intensity exercise remained elevated throughout the first recovery window (0:00-14:50mins).

The third hypothesis stated: as compared to a non-exercise control, following both handgrip exercise protocols there will be augmentations to resting forearm blood flow without differences in peak reactive hyperaemic flow. Key Findings: The hypothesis was rejected as neither HG exercise design resulted in alterations to resting or peak blood flows (p>0.05).

In summary, this study demonstrated that older, normotensive, post-menopausal women have dissimilar acute cardiovascular responses to two HG exercise bouts with different protocol design.
features. As compared to moderate-intensity sustained HG exercise, high intensity interval HG exercise elicits augmented instantaneous elevations in BP which return to day-of resting values within the first fifteen minutes of exercise recovery.

The second study (Chapter 4) described the full comprehensive design and evaluation of the Maximal INTe rval (MINT) handgrip exercise strategy. Part 1 of this research was dedicated to the MINT exercise protocol, beginning with the theoretically driven conceptualization of a highly accessible exercise option for at-home exercise training that considered the unique physiological responses of older women to HG exercise. Part 2 of this research described a product development opportunity that arose as a result of participant feedback from Part 1 that identified a need for a handgrip tool that would be better suited for maximal grip contractions. The creation of the MINT grip tool began with a mixed-methods assessment of participant opinions regarding two distinct in-laboratory grip tools. These qualitative and quantitative opinions informed the creation of four unique mock-MINT tools that were critiqued and compared against not only each other but also against the original two in-laboratory tools by structured focus groups. **In summary, this study demonstrated that the MINT exercise protocol elicits substantial, yet safe, BP elevations among cohorts of older, post-menopausal women with both normotensive resting BPs and above-optimal resting BPs. In addition, the participant-informed new product development process resulted in the design of a novel grip tool. Together, the MINT protocol and MINT grip tool represent the MINT handgrip strategy, ready to be critically assessed for both efficacy and effectiveness.**

The third study (Chapter 5) used a prospective cohort design to explore the physiological efficacy and behavioural effectiveness of the MINT exercise strategy. Physiological efficacy was explored by assessing the time course of cardiovascular alterations throughout an 8-week training intervention. Cardiovascular alterations of interest were resting systolic BP, diastolic BP, and HR. Additional physiological variables of interest include those that have been proposed as mediators of BP changes: a neurocardiac index of autonomic nervous control (heart rate variability (HRV)), indicators of arterial structure (radial augmentation index (Aix), and carotid-radial pulse wave velocity (crPWV)). Behavioural effectiveness was explored by assessing at-home exercise adherence patterns, exercise enjoyment, and qualitative indicators of anticipated/actual barriers to exercise. The **first hypothesis** stated: high intensity handgrip exercise training will cause reductions in resting blood pressure but not heart rate. **Key Findings:** In support of this hypothesis, MINT handgrip exercise was shown to elicit significant reductions to resting systolic BP at both the 4week follow-up and 8week
follow-up. This hypothesis was rejected in that resting diastolic BP values remained unchanged throughout the training, and that resting HR was significantly reduced at the 4week follow-up.

The second hypothesis stated: although participants would anticipate barriers of ‘time’ and ‘habit’, they would nonetheless demonstrate high exercise adherence to MINT exercise. **Key Findings:** In support of this hypothesis, nearly one half of participants anticipated that the barrier of ‘habit’ and nearly one quarter anticipated that the barrier of ‘time’ specifically would influence their ability to adequately comply with the exercise schedule. Despite this anticipated barriers, compliance to the at-home training throughout the eight weeks was extremely high.

The third hypothesis stated: eight weeks of handgrip training will result in shifts to neurocardiac measures that align with parasympathetic preponderance while indices of arterial structure will remain unchanged. **Key Findings:** In support of this hypothesis, eight weeks of MINT training increased measures of sample entropy, a non-linear index of heart rate complexity. Furthermore, measures of arterial structure, including augmentation index and pulse wave velocity, remained unchanged throughout the handgrip training intervention.

**In summary, this study demonstrated both exercise efficacy and exercise effectiveness of the MINT handgrip exercise strategy.** Exercise efficacy was shown through via the physiological improvements to both resting systolic BP and heart rate complexity. Exercise effectiveness was demonstrated via high exercise adherence despite perceived exercise barriers of ‘habit’ and ‘time’.

The fourth and final study (Chapter 6) used a prospective cohort design to explore the inter-individual variability of handgrip-induced training responses using cardiovascular reactivity. Not only was the potential for one’s cardiovascular reactivity to predict future training-induced blood pressure reductions determined, but the ability of MINT exercise training to lower one’s reactivity to psychophysiological stressors was also examined.

The first hypothesis stated: cardiovascular reactivity to a serial subtraction stressor and a handgrip stressor would predict training reductions. **Key Findings:** This hypothesis was rejected, as a robust relationship between reactivity measures and residualized systolic blood pressure change scores was not determined.

The second hypothesis stated: exercise training will elicit similar attenuations of cardiovascular reactivity to both a serial subtraction stressor and a handgrip stressor. **Key Findings:** This hypothesis was rejected, as the handgrip exercise training elicited dissimilar alterations of the cardiovascular reactivity to the two stressors. Training resulted in reduced reactivity to serial subtraction, yet enhanced reactivity to handgrip stressor.
In summary, the cardiovascular reactivity of post-menopausal women to two psychophysiological stressors is unable to confirm previous research that used this reactivity to explore the inter-individual variability of blood pressure responses. The dissimilar impact of handgrip training on the reactivity responses between the two stressors should be read with caution, as the success of the handgrip exercise training intervention to improve grip strength may have influenced the handgrip stressor outcomes.

7.2 Limitations

This thesis is not without limitations. First and foremost, there are notable limitations to data collection techniques. The technical issues with the Suunto heart rate system resulted in substantial loss. The entire planned assessment of HRV from Chapter 3 was dropped. It was hoped that we would have been able to complete assessments of non-linear Sample Entropy, as others have shown that an acute handgrip exercise bout results in post-exercise improvements in Sample Entropy among older hypertensives (Millar et al., 2013). Furthermore, approximately half of the participants from Chapter 5 were removed from analysis as well. Despite this loss of data, we were still able to show that eight weeks of MINT handgrip training favourably impacted non-linear Sample Entropy in a cohort of older women, representing a robust training effect. An additional technical issue was the Finapres system, which uses a photoplethysmograph under a pressure cuff to detect arterial pulsation. Outputs of the plethysmograph are used to drive a servo-loop, which rapidly changes the cuff pressure to keep the output constant, resulting in the local vasculature being held partially open (Pickering et al., 2005). Although change scores as calculated from the Finometer output are accurate, absolute values are known to be over- or under-estimated, depending on the person (Pickering et al., 2005). We accounted for this in all research designs by only using change scores as calculated by Finometer. All reported absolute scores are therefore change scores added to day-of resting (as calculated by BpTRU).

Although this thesis purposefully sought out to isolate and study older women specifically, the results of this research have subsequently limited transferability to other populations.

The biggest research limitation from the long-term training assessment (Chapter 5 and 6) is that we relied heavily on the honesty of research participants regarding exercise adherence and compliance. We have no way of determining if women actually completed the exercises or if they were misleading us on their tracking forms. The significance of this may be quite impactful to the research results. Perhaps, the insignificant results we reported pertaining to the lack of a training-induced difference in resting diastolic
blood pressure, heart rate, augmentation index, and pulse wave velocity may be false. Alternatively, perhaps the resting systolic blood pressure and heart rate complexity scores merely represented highly modifiable traits. That being said, not only was the average grip strength improved in the non-dominant hand only, the average grip performance during the in-laboratory completion of MINT was also augmented. As such, we can say with relatively strong certainly that at least some of the prescribed at-home training was being completed.

7.3 Future Research Studies

Throughout each of the four studies in this thesis opportunities for future research have been identified in the discussion portions. To avoid duplication, those have not been repeated. Instead, future research studies that would more holistically extend from this thesis have been presented.

Although researchers have used handgrip as a stimuli to assess hemodynamic behaviour since the mid-1970s (Martin et al., 1974; Nagle, Seals, & Hanson, 1988; Seals, Washburn, Hanson, Painter, & Nagle, 1983; Seals, Chase, &Taylor, 1988), the last ten to fifteen years have really seen a surge of handgrip exercise as a training modality for resting blood pressure reduction (Araujo et al., 2011). As we continue to use this surprisingly effective exercise stimulus, future assessments of the potentially unique training responses of individual cohorts may help us to better understand the mechanistic influences resulting in these favourable cardiovascular adaptations.

As discussed throughout this thesis, post-menopausal women have been shown to have an enhanced exercise pressor response to handgrip exercise which appears to be mediated by an enhanced metaboreflex (Choie et al., 2012). Sustained handgrip exercise of >20%MVC limits local muscular blood flow (Barcroft & Millen, 1939; Barnes, 1980; Donald et al., 1967) and may not only lead to the creation of vasoactive metabolites but may also limit their removal. As such, handgrip exercise training interventions that prescribe regular use of moderate-intensity handgrip training may find that older women do not react with such dramatic reductions. Furthermore, handgrip exercise training has been shown to improve heart rate complexity with sex-specific comparison of responses still to be completed. Although the exact combination of physiological mechanisms responsible for the aforementioned dramatic reduction in resting BP remains to be fully elucidated, researchers have proposed both favourable modifications to the autonomic control of cardiac and vascular structures (Lawrence et al., 2015; Millar et al, 2014) and improvements in vascular resistance (Carlson et al., 2014) as potential
mediators. If properly coordinated, one study could be robust enough as to address all of these remaining questions at the same time.

Utilizing a large randomized controlled trial, the sexual dimorphism of the physiological responses to handgrip exercise training interventions could be thoroughly explored. This robust study would have four primary research objectives: (1) to explore the influence of biological sex on the handgrip-induced training responses of resting blood pressure and resting heart rate, (2) to explore the influence of handgrip intervention design features by comparing high-intensity intermittent handgrip exercise (MINT) to moderate-intensity sustained handgrip exercise (ZONA), (3) to explore the interaction between biological sex and handgrip intervention design, and (4) to explore proposed mechanistic drivers to the BP response. In completing this proposed research, recruitment of both post-menopausal women and age-matched men would occur with all participants being randomly assigned to 10 weeks of either ZONA handgrip training, MINT handgrip training, or a sham exercise protocol. Biweekly laboratory visits for physiological assessments would reveal time-dependent changes in all collected variables, leading to a comprehensive understanding of various mechanistic roles.

7.4 Conclusions

Data from this thesis supports the use of the Maximal INTerval (MINT) handgrip exercise strategy for at-home training among older women. The initial, theoretically driven, design of the MINT exercise protocol considered the unique physiological responses of older women to handgrip exercise. In addition, while progressing through stages of new product development for the ultimate design of the MINT grip tool, participant opinions were incorporated at each step to ensure that the final product was informed by the preferences of this specific cohort directly. An acute bout of MINT exercise results in instantaneous perturbations to blood pressures that return to day-of resting values immediately. Furthermore, eight weeks of at-home exercise training is able to successfully reduce resting systolic blood pressure and improve heart rate complexity. The insignificant association between MINT-induced blood pressure reduction and measures of cardiovascular reactivity highlight the unique autonomic responses of this cohort and further support the need for robust future assessments of sex-specific training responses to handgrip exercise.
References


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Higashi, Y., Sasaki, S., Nakagawa, K., Matsuura, H., Kajiyama, G., & Oshima, T. (2001). A noninvasive measurement of reactive hyperemia that can be used to assess resistance artery endothelial function in humans. *American Journal of Cardiology, 87*(1), 121-125, A129.


APPENDIX 1a

Acute Study (Chapter 3) Online Recruitment

Call For Research Participants, Post-Menopausal Women with Slightly High Blood Pressure

The Human Performance and Physiology lab is currently recruiting post-menopausal women to participate in a study looking at the impact of handgrip exercise on the health of the arteries and veins. Participants must be free from cardiovascular disease (no previous heart attacks or strokes, etc.), currently not taking regular medication (either for blood pressure control or for hormone replace therapy), and have slightly high resting blood pressure (more than 120/80mmHg).

Full participation requires that participants visit the University of Toronto Athletic Center (55 Harbord st.) five times, with each visit lasting approximately 1.5 hours. During the visit participants will complete handgrip exercise followed by non-invasive measurements of vascular health (looking at the veins and the arteries).

As compensation for your time, participants will receive either (your-choice) a three-month gym membership to the Athletic Centre or a $50 dollar gift card. Participants will also have all travel costs (ie. parking or TTC costs) reimbursed.

If interested please email cardiovascularstudy@gmail.com or call 416-978-0762 to receive more information.
APPENDIX 1b

Acute Study (Chapter 3) Study Poster

University of Toronto
Faculty of Kinesiology and Physical Education

WOMEN’S HEALTH RESEARCH

Cardiovascular disease is the number one killer of older women. Researchers at the University of Toronto are trying to determine ways of controlling risk factors so that the burden of cardiovascular disease can be reduced.

We are currently recruiting women to help us understand the impact of handgrip exercise on the health of blood vessels.

Enrolled participants will be invited to the Cardiovascular and Health Lab (55 Harbord st) to complete 5 visits, each visit will last approx. 1.5–2.0 hours. All measurements are non-invasive.

All participants will be compensated for their time!

We are recruiting women who meet these criteria:

- At least 1 year postmenopausal (more than 1 year since last menstrual cycle)
- Have normal to slightly high blood pressure, (blood pressure around 115-139/75-89 mmHg). Not to worry if you are unsure of your blood pressure, we will measure it on your first visit.
- Not currently taking any hormone medication (for example, estrogen pills) or medication to control blood pressure.
- Not have cardiovascular disease (such as hypertension, stroke, heart attack)
- Be a non-smoker (at least 5 years since last cigarette)
- Right handed

UofT Health Research. 416-978-0762
cardiovascularstudy@gmail.com
APPENDIX 1c

Acute Study (Chapter 3) Initial Information to Inquiring Participants

Email:

Good (morning)(afternoon)(evening) ___.

Thank you for your email, and for your interest!
We are very excited about our current research project. In brief, we are currently recruiting post-menopausal women with normal to slightly high blood pressure to participate in an in-laboratory series of research studies. For a full description of the project including compensation details, please see the attached document. If you find that you have any questions please do not hesitate to contact me. I can be reached via email (cardiovascularstudy@gmail.com) or by phone at 416-946-5637.

Once you have read through the attached document if you remain interested in participation then we can move on to discussing schedules. We are currently booking in participants for initial sessions for next week. All sessions occur in the afternoon/evening and are scheduled based on the availability of the lab space.

If you have decided that you would like to come to the lab and learn a bit more about the project goals and objectives please let me know and I would be happy to send you the available lab spots for next week. Alternatively, we also have space available later the following week.

Please do not hesitate to ask me about any questions or concerns you may have. I am happy to help clarify them!

Thank you again for your interest. I am looking forward to hearing from you. I hope you have a lovely evening,

Danielle Bentley, primary investigator
PhD Candidate
University of Toronto
Thank you for expressing your interest in research participation. The Human Health and Performance laboratory at the University of Toronto is very grateful to all of our research participants!

We are currently recruiting postmenopausal women with the following inclusion criteria. Women must:

- be at least one year since last menstrual bleed
- have normal to slightly high blood pressure, (blood pressure around 115-139 / 75-89 mmHg).
  Not to worry if you are unsure of your blood pressure, we will measure it on your first visit.
- not be currently taking any hormone medication (for example, estrogen pills)
- not be currently taking any medication to control blood pressure
- not have cardiovascular disease (such as hypertension, stroke, heart attack)
- be a non-smoker (at least 5 years since last cigarette)
- right handed

The current study involves non-invasive measurements of blood vessel health using pressure cuffs placed on the arm. These non-invasive measurements will be taken before and after a bout of handgrip exercise that will last between 6-13 minutes. The entire study will be fully explained and demonstrated on your first lab visit, with ample time for you to ask questions and gain clarification.

Full study participation requires 5 visits to the Human Health and Performance laboratory within the University of Toronto Athletic Centre (55 Harbord street, at the southeast corner of Harbord and Spadina). Each visit will last approximately 1.5-2.0hrs and can be scheduled between 2:00pm to 8:00pm all days of the week. When determining what time would be most convenient for you, please keep in mind these few points. Prior to each visit you must complete a 4hr fast, a 4hr abstinence from caffeine, and a 24hr abstinence from alcohol and strenuous exercise.

As compensation for your time, you will be given the opportunity to choose either a three-month gym membership (valued at $243.00) to the University of Toronto Athletic Centre or a $50 dollar gift card upon completion of your final session. You will also be able to claim travel expenses up to $30.00 (such as parking meter or TTC). Finally, you may have the opportunity to participate in an additional research study which can extend your gym membership to a total of 9 months.

If you have any further questions or concerns please do not hesitate to ask me. Thank you again for your interest and I am looking forward to hearing from you.

Sincerely,

Danielle Bentley, PhD Candidate and Principal Investigator
Faculty of Kinesiology and Physical Education
University of Toronto
Good (morning)(afternoon)(evening) ____.

This is a friendly reminder of your final research study session tomorrow, (date) at (time). The visit will last approx. 2.0 hours. I will meet you in the main lobby of the University of Toronto Athletic Center (55 harbord st. southeast corner of Harbord and Spadina), near the large windows that overlook the swimming pool. Please give the lab a call when you get there!

Please remember to wear comfortable clothes, including a short sleeved t-shirt. This way we can take blood pressure readings. As a final note, to control for the impact of certain factors we ask that you please remember the following points. Please refrain from food and caffeine for 4 hours, and strenuous exercise and alcohol for 24 hours.

If you have any final questions the lab phone number is 416-978-0762.

Thank you again for your interest! Looking forward to seeing you tomorrow,

Danielle Bentley, primary investigator
PhD Candidate
University of Toronto
APPENDIX 1e

Focus Group (Chapter 4) Call For Participants

Good (morning)(afternoon)(evening) ____,

You are receiving this email because of your previous inquiry and/or participation in research at the University of Toronto’s Cardiovascular Health and Performance Laboratory.

We are continuing to make progress in our understanding of handgrip exercise as a novel form of exercise to regulate blood pressure in post-menopausal women. As a result, we are recruiting for one final research project!

We would like you to consider participating in our study – to provide user feedback regarding our new and improved handgrip tools.

Study details (study document attached):
- You will attend one group feedback session (~1 hour).
- You will complete a feedback form, commenting on the colour, shape, size, and grip of 4 different handgrip tools.
- **Compensation:** travel expenses will be compensated (1.5h parking (with receipt) or 2 TTC transit tokens). In addition, you will receive a $5.00 giftcard to either Tim Hortons or Starbucks as a token of appreciation.

Feedback sessions are currently being scheduled for **Tue May 19th at 6pm, Wed May 20th at 2pm, or Thursday May 21 at 9:30am.** Alternatively, if you are interested in providing feedback but unable to attend one of the group sessions we will do our very best to arrange a time that best suits your schedule.

If you are interested in participating, please contact me via email (danielle.bentley@mail.utoronto.ca) or phone (416-946-5637) to schedule your visit

Thank you in advance and I look forward to hearing from you,

Danielle Bentley, primary investigator
PhD Candidate
University of Toronto
APPENDIX 1f

Focus Group (Chapter 4) Reminder Email Template

Good (morning)(afternoon)(evening) ___,

This is a friendly reminder of your research participation for tomorrow, (date), from (times). The session will be held at the new Goldring Centre for High Performance Sport located at 100 Devonshire place (close to the west side of the UofT football field). Enter the Goldring Centre in the north doors and take the elevator up to the fourth floor, room 443. There will be signs helping guide in the right direction!

During the hour you will be in a small group and providing feedback about four different handgrip tools that I created. I want to know about how you like the shapes, colours, grip material, etc. Your feedback will be directly used in creating a final handgrip tool for future use in long-term training projects.

Looking forward to seeing you tomorrow. I am so grateful for your participation!! Thank you!!

If for any reason you need to get a hold of me I can be reached at 416-276-2355.

Danielle Bentley, primary investigator
PhD Candidate
University of Toronto
Call For Research Participants, Post-Menopausal Women with Slightly High Blood Pressure

The Human Performance and Physiology lab is currently recruiting post-menopausal women to participate in a study looking at the impact of handgrip exercise on the health of the arteries and veins. Participants must be free from cardiovascular disease (no previous heart attacks or strokes, etc.), and have slightly high resting blood pressure (more than 120/80mmHg).

Full participation requires that participants visit the University of Toronto Athletic Center (55 Harbord st.) four times, with each visit lasting approximately 1.5 hours. In addition to laboratory visits you will be asked to completed at home handgrip exercise that will take approximately 20 minutes per week.

You will be compensated for your time.

If interested please email cardiovascularstudy@gmail.com or call 416-276-2355 to receive more information.
APPENDIX 1h

Long-term Training Study (Chapter 5 and Chapter 6) Study Poster

University of Toronto
Faculty of Kinesiology and Physical Education

WOMEN’S HEALTH RESEARCH

Cardiovascular disease is the number one killer of older women. Researchers at the University of Toronto are trying to determine ways of controlling risk factors so that the burden of cardiovascular disease can be reduced.

We are currently recruiting women to help us understand the impact of handgrip exercise on the health of blood vessels.

Enrolled participants will be invited to the Health and Performance Lab (100 Devonshire Pl) to complete 8 weeks of at-home handgrip exercise training.

All participants will be compensated for their time!

We are recruiting women who meet these criteria:

- At least 3 years postmenopausal (more than 3 years since last menstrual cycle)
- Have slightly high blood pressure, (blood pressure around 121-139 / 81-89 mmHg). Not to worry if you are unsure of your blood pressure, we will measure it on your first visit.
- Are not currently taking any hormone medication (for example, estrogen pills).
- Do not have cardiovascular disease (such as hypertension, stroke, heart attack)
- Do not smoke (at least 5 years since last cigarette)

UofT Health Research. 416-276-2355 cardiovascularstudy@gmail.com
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UofT Health Research. 416-276-2355 cardiovascularstudy@gmail.com
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UofT Health Research. 416-276-2355 cardiovascularstudy@gmail.com
APPENDIX 1i

Long-term Training Study (Chapter 5 and Chapter 6) Initial Information to Inquiring Participants

Email:

Good (morning)(afternoon)(evening) ___.

Thank you for your email, and for your interest!
We are very excited about our current research project. In brief, we are currently recruiting post-menopausal women with slightly high blood pressure to participate in an at-home handgrip exercise training program. For a full description of the project including compensation details, please see the attached document. If you find that you have any questions please do not hesitate to contact me. I can be reached via email (cardiovascularstudy@gmail.com) or by phone at 416-946-5637.

Once you have read through the attached document if you remain interested in participation than we can move on to discussing schedules. We are currently booking in participants for initial sessions for next week. All sessions occur in the afternoon/evening and are scheduled based on the availability of the lab space.

If you have decided that you would like to come to the lab and learn a bit more about the project goals and objectives please let me know and I would be happy to send you the available lab spots for next week. Alternatively, we also have space available later the following week.

Please do not hesitate to ask me about any questions or concerns you may have. I am happy to help clarify them!

Thank you again for your interest. I am looking forward to hearing from you. I hope you have a lovely evening,

Danielle Bentley, primary investigator
PhD Candidate
University of Toronto
Thank you for expressing your interest in research participation. The Human Health and Performance laboratory at the University of Toronto is very grateful to all of our research participants!

We are currently recruiting postmenopausal women with the following inclusion criteria. Women must:

- be at least three years since last menstrual bleed
- have normal to slightly high blood pressure, (blood pressure around 120-139 / 80-89 mmHg). Not to worry if you are unsure of your blood pressure, we will measure it on your first visit.
- not be currently taking any hormone medication (for example, estrogen pills)
- no previous or current cardiovascular disease (such as hypertension, stroke, heart attack)
- not a current smoker (at least 5 years since last cigarette)

The current study involves eight weeks of at-home handgrip exercise training. You will be given a handgrip device, asked to complete 5 minutes of training 4/week, and asked to record your training performance using an online tracking system.

In addition to the at-home exercise training, full study participation requires 4 visits to the Human Health and Performance laboratory within the Goldring Centre for High Performance Sport (100 Devonshire Pl. at the southwest corner of Bloor and Bedford). The 4 visits are scheduled as follows: visit1 and visit2 occur at the very beginning of the study, visit3 at the midway point (week four) and visit4 at the end of the study.

Each visit will last approximately 1.5hrs and can be scheduled between 2:00pm to 8:00pm all days of the week. When determining what time would be most convenient for you, please keep in mind that prior to each visit you must complete a 4hr fast, a 4hr abstinence from caffeine, and a 24hr abstinence from alcohol and strenuous exercise.

As compensation for your time, you will receive $100.00 cash ($30.00 at the midway point and $70.00 at the end). You will also be eligible to select either a two-month gym membership (valued at $162.00) to the University of Toronto athletic facilities or a $50 dollar gift card upon completion of your final session.

If you have any further questions or concerns please do not hesitate to ask me. Thank you again for your interest and I am looking forward to hearing from you to schedule your first lab visit!

Sincerely,

Danielle Bentley, PhD Candidate and Principal Investigator
Faculty of Kinesiology and Physical Education
University of Toronto
APPENDIX 1j

Long-term Training Study (Chapter 5 and Chapter 6) Reminder (Initial Visit) Email Template

Good (morning)(afternoon)(evening) ___.

This is a "friendly reminder" about your final research visit tomorrow (Date) at (Time am/pm). Please note, the visit will last for approximately 1.5 hours.

The visit will occur in the Goldring Centre for High Performance Sport, room 415. This is the same place as before. The address is 100 Devonshire place.

I see that you have updated your log sheet. Wonderful! You are all done your at-home handgrip training! Thank you for all your wonderful work throughout the last 2 months!

I would also like to remind you about our study restrictions. Please refrain from food and caffeine for 4hrs prior to the start of your visit. Please refrain from alcohol and strenuous activity for 24hrs prior to the start of your visit.

At the end your visit tomorrow you will receive your final compensation. This includes the remaining $70.00 cash. In addition, we also extend our thanks by offering you the choice of selecting either a three-month gym membership to the UofT facilities OR a $50.00 gift card (typically to either Tim Hortons or Starbucks). Just so that I can be sure to have everything ready for you, it would be very helpful for me to know if you would like the gym membership or the gift card (and to which establishment).

If you think of any other questions I would be happy to answer them via email. Also, if for any reason you would like to get a hold of me directly my cell phone number is 416-276-2355.

I hope you have had an enjoyable week thus far,

Cheers,

Danielle Bentley, primary investigator
PhD Candidate
University of Toronto
APPENDIX 1k

Long-term Training Study (Chapter 5 and Chapter 6) 2-week Follow-up Template

Good (morning)(afternoon)(evening) ____,

You are officially two weeks in to your handgrip training, and you are doing great!

This email is a follow-up to see how everything has been going. Now that you have been able to establish a little bit of a routine, have you been having any trouble with the grip device, timing, or tracking?
As always, I am very happy to help with any concerns you may have!

As a friendly reminder, the handgrip device is to be used 4 times per week, by the non-dominant hand only, as 32 separate 5 second squeezes (as hard as you can) with 5 seconds of rest in between. It should take just over 5 minutes each time you use it. If for any reason that is not what you have been doing, please let me know. I will document the deviation and help you back on track!

I am looking forward to seeing you for your half way visit. Based on your start date we should be scheduling this session for sometime between (Date 1) – (Date 3). Here are the available options for your visit.

Date 1
2:00-3:30pm
3:30-5:00pm
5:00-6:30pm
6:30-8:00pm

Date 2
2:00-3:30pm
3:30-5:00pm
5:00-6:30pm
6:30-8:00pm

Date 3
2:00-3:30pm
3:30-5:00pm
5:00-6:30pm
6:30-8:00pm

Thank you again for your continued support of this exciting research. Keep up the great work and I look forward to hearing from you!

Danielle Bentley, primary investigator
PhD Candidate University of Toronto
Good (morning)(afternoon)(evening) ____,

I hope that your week has gone well so far (it's absolutely beautiful out!). You are officially six weeks in to your handgrip training, and you are doing great!

This email is a follow-up to see how everything has been going. Now that you are nearing the end of everything have been able to establish a little bit of a routine, do you have any final concerns regarding the grip device, timing, or tracking form? As always, I am very happy to help with any concerns you may have!

As a friendly reminder, the handgrip device is to be used 4 times per week, by the non-dominant hand only, as 32 separate 5 second squeezes (as hard as you can) with 5 seconds of rest in between. It should take just over 5 minutes each time you use it. If for any reason that is not what you have been doing, please let me know. I will document the deviation and help you back on track!

I am looking forward to seeing you for your final way visit. It would be wonderful to confirm a date and time for that visit. Based on your exercise start date I would like to have you come in to the between (Date 1) and (Date 3). For those dates I currently have:

Date 1
2:00-3:30pm
3:30-5:00pm
5:00-6:30pm
6:30-8:00pm

Date 2
2:00-3:30pm
3:30-5:00pm
5:00-6:30pm
6:30-8:00pm

Date 3
2:00-3:30pm
3:30-5:00pm
5:00-6:30pm
6:30-8:00pm

Thank you again for your continued support of this exciting research. Great job so far and I look forward to hearing from you!

Danielle Bentley, primary investigator
PhD Candidate University of Toronto
APPENDIX 1m

Long-term Training Study (Chapter 5 and Chapter 6) Missing Online Tracking Information Follow-up Example

Good (morning)(afternoon)(evening) ____ ,

I hope you had a wonderful weekend! It really is beautiful out there :)

Just a friendly reminder to please update your exercise log book whenever you have a minute or two. Hard to believe that we are so close to the end. Only one more week to go!!

All the best,

Danielle Bentley, primary investigator
PhD Candidate
University of Toronto
APPENDIX 2a

Physical Activity Readiness Questionnaire Plus

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.

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Has your doctor ever said that you have a heart condition OR high blood pressure?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Do you feel pain in your chest at rest, during your daily activities of living, or when you do physical activity?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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 overbreathing (including during vigorous exercise).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Have you ever been diagnosed with another chronic medical condition (other than heart disease or high blood pressure)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Are you currently taking prescribed medications for a chronic medical condition?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Has your doctor ever said that you should only do medically supervised physical activity?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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, or 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.
### SECTION 2 - CHRONIC MEDICAL CONDITIONS

Please read the questions below carefully and answer each one honestly: check YES or NO.

<table>
<thead>
<tr>
<th>Question</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you have Arthritis, Osteoporosis, or Back Problems?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1c. Have you had steroid injections or taken steroid tablets regularly for more than 3 months?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Do you have Cancer of any kind?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2a. Does your cancer diagnosis include any of the following types: lung/bronchogenic, multiple myeloma (cancer of plasma cells), head, and neck?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2b. Are you currently receiving cancer therapy (such as chemotherapy or radiotherapy)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Do you have Heart Disease or Cardiovascular Disease?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3b. Do you have an irregular heart beat that requires medical management? (e.g. atrial brillation, premature ventricular contraction)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3c. Do you have chronic heart failure?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3e. Do you have diagnosed coronary artery (cardiovascular) disease and have not participated in regular physical activity in the last 2 months?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Do you have any Metabolic Conditions? This includes Type 1 Diabetes, Type 2 Diabetes, Pre-Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4a. Is your blood sugar often above 130 mmol/L? (Answer YES if you are not sure)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4c. Do you have other metabolic conditions (such as thyroid disorders, pregnancy-related diabetes, chronic kidney disease, liver problems)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5b. Do you also have back problems affecting nerves or muscles?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Please read the questions below carefully and answer each one honestly: check YES or NO.

<table>
<thead>
<tr>
<th>Question</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Do you have a Respiratory Disease? This includes Chronic Obstructive Pulmonary Disease, Asthma, Pulmonary High Blood Pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6d. Has your doctor ever said you have high blood pressure in the blood vessels of your lungs?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Do you have a Spinal Cord Injury? This includes Tetraplegia and Paraplegia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7b. Do you commonly exhibit low resting blood pressure significant enough to cause dizziness, light-headedness, and/or fainting?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7c. Has your physician indicated that you exhibit sudden bouts of high blood pressure (known as Autonomic Dysreflexia)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Have you had a Stroke? This includes Transient Ischemic Attack (TIA) or Cerebrovascular Event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8b. Do you have any impairment in walking or mobility?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8c. Have you experienced a stroke or impairment in nerves or muscles in the past 6 months?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Do you have any other medical condition not listed above or do you live with two chronic conditions?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9b. Do you have a medical condition that is not listed (such as epilepsy, neurological conditions, kidney problems)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9c. Do you currently live with two chronic conditions?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 46 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 professional, 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 designee) may retain a copy of this form for their records. In these instances, the Trustee will be required to adhere to local, national, and international guidelines regarding the storage of personal health information ensuring that they maintain the privacy of the information and do not misuse or wrongly 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

The PAR-Q+ was created using the evidence-based AGREE process (1) by the PAR-Q+Collaboration chaired by Dr. Darren E. R. Warbuton with Dr. Norain Gledhill, Dr. Veronica Jamnik, and Dr. Donald C. McKerinner (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.
APPENDIX 2b

Rapid Assessment of Physical Activity

<table>
<thead>
<tr>
<th>How physically active are you?</th>
<th>Does this accurately describe you?</th>
</tr>
</thead>
<tbody>
<tr>
<td>I rarely or never do any physical activities.</td>
<td>Yes ☐ No ☐</td>
</tr>
<tr>
<td>I do some <strong>light</strong> or <strong>moderate</strong> physical activities, but not every week.</td>
<td>Yes ☐ No ☐</td>
</tr>
<tr>
<td>I do some <strong>light</strong> physical activity every week.</td>
<td>Yes ☐ No ☐</td>
</tr>
<tr>
<td>I do <strong>moderate</strong> physical activities every week, but less than 30 minutes a day or 5 days a week.</td>
<td>Yes ☐ No ☐</td>
</tr>
<tr>
<td>I do <strong>vigorous</strong> physical activities every week, but less than 20 minutes a day or 3 days a week.</td>
<td>Yes ☐ No ☐</td>
</tr>
<tr>
<td>I do 30 minutes or more a day of <strong>moderate</strong> physical activities, 5 or more days a week.</td>
<td>Yes ☐ No ☐</td>
</tr>
<tr>
<td>I do 20 minutes or more a day of <strong>vigorous</strong> physical activities, 3 or more days a week.</td>
<td>Yes ☐ No ☐</td>
</tr>
<tr>
<td>I do activities to increase muscle <strong>strength</strong>, such as lifting weights or calisthenics, once a week or more.</td>
<td>Yes ☐ No ☐</td>
</tr>
<tr>
<td>I do activities to improve <strong>flexibility</strong>, such as stretching or yoga, once a week or more.</td>
<td>Yes ☐ No ☐</td>
</tr>
</tbody>
</table>

ID # _____________________________
Today’s Date _______________________
APPENDIX 2c

Cardiovascular Risk Factors

UNIVERSITY OF TORONTO
Faculty of Kinesiology and Physical Education

Subject ID: 

Acute Alterations in Blood Pressure and Potential Mechanisms Following Handgrip Exercise

Principle Investigator:
Danielle Bentley, PhD Candidate, Department of Exercise Science, University of Toronto

Supervisor:
Dr. Scott Thomas, Department of Exercise Science, University of Toronto

Please Select (YES) or (NO)

1. Are you a male?
   - Yes
   - No

2. Are you older than 65 years?
   - Yes
   - No

3. Do you have a family history of heart disease (defined as a first degree blood relative)?
   - Yes
   - No

4. Are you African, Mexican, Indian, Hawaiian?
   - Yes
   - No

5. Are you a current smoker?
   - Yes
   - No

6. Do you currently have high cholesterol?
   - Yes
   - No

7. Do you currently have high blood pressure?
   - Yes
   - No

8. Do you currently have diabetes mellitus?
   - Yes
   - No

9. Do you currently consume an unhealthy diet?
   - Yes
   - No

10. Are you under a high degree of daily stress?
    - Yes
    - No

11. Do you consume a great amount of alcohol?
    - Yes
    - No

DO NOT COMPLETE
Current Inactive?
- Yes
- No

Currently Overweight/Obese (BMI > 30)?
- Yes
- No

Total Non-Modifiable? 
- Total Modifiable?
- /4
- /4
APPENDIX 2d

State Trait Anxiety Inventory

State-Trait Anxiety Inventory for Adults

Self-Evaluation Questionnaire
STAI Form Y-1 and Form Y-2

Developed by Charles D. Spielberger
in collaboration with R.L. Gorsuch, R. Lushene, P.R. Vagg, and G.A. Jacobs

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www.mindgarden.com

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SELF-EVALUATION QUESTIONNAIRE [STAI] Form Y-1

Please provide the following information:
Name________________________ Date________ S____

Age________________________ Gender (Circle) M F T____

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

1. I feel calm________________________________________ 1 2 3 4
2. I feel secure________________________________________ 1 2 3 4
3. I am tense__________________________________________ 1 2 3 4
4. I feel strained_______________________________________ 1 2 3 4
5. I feel at ease________________________________________ 1 2 3 4
6. I feel upset__________________________________________ 1 2 3 4
7. I am presently worrying over possible misfortunes__________ 1 2 3 4
8. I feel satisfied_______________________________________ 1 2 3 4
9. I feel frightened______________________________________ 1 2 3 4
10. I feel comfortable___________________________________ 1 2 3 4
11. I feel self-confident_________________________________ 1 2 3 4
12. I feel nervous_______________________________________ 1 2 3 4
13. I am jittery__________________________________________ 1 2 3 4
14. I feel indecisive______________________________________ 1 2 3 4
15. I am relaxed_________________________________________ 1 2 3 4
16. I feel content_______________________________________ 1 2 3 4
17. I am worried_________________________________________ 1 2 3 4
18. I feel confused_______________________________________ 1 2 3 4
19. I feel steady_________________________________________ 1 2 3 4
20. I feel pleasant_______________________________________ 1 2 3 4

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Published by Mind Garden, Inc., 1690 Woodside Rd, Suite 202, Redwood City, CA 94061
www.mindgarden.com
SELF-EVALUATION QUESTIONNAIRE
STAI Form Y-2

Name________________________________________ Date__________________

DIRECTIONS
A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you generally feel. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

21. I feel pleasant................................................................. 1 2 3 4
22. I feel nervous and restless ........................................... 1 2 3 4
23. I feel satisfied with myself............................................... 1 2 3 4
24. I wish I could be as happy as others seem to be .............. 1 2 3 4
25. I feel like a failure............................................................. 1 2 3 4
26. I feel rested..................................................................... 1 2 3 4
27. I am "calm, cool, and collected"........................................ 1 2 3 4
28. I feel that difficulties are piling up so that I cannot overcome them........................................... 1 2 3 4
29. I worry too much over something that really doesn't matter.......................... 1 2 3 4
30. I am happy..................................................................... 1 2 3 4
31. I have disturbing thoughts.................................................. 1 2 3 4
32. I lack self-confidence......................................................... 1 2 3 4
33. I feel secure..................................................................... 1 2 3 4
34. I make decisions easily....................................................... 1 2 3 4
35. I feel inadequate............................................................... 1 2 3 4
36. I am content..................................................................... 1 2 3 4
37. Some unimportant thought runs through my mind and bothers me.................. 1 2 3 4
38. I take disappointments so keenly that I can't put them out of my mind............. 1 2 3 4
39. I am a steady person.......................................................... 1 2 3 4
40. I get in a state of tension or turmoil as I think over my recent concerns and interests .................................................. 1 2 3 4

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APPENDIX 2e

Research Compliance Quiz

Compliance Quiz

When did you last eat food? __________
When did you last consume caffeine? __________
When did you last consume alcohol? __________
When did you last participate in strenuous exercise? __________
APPENDIX 2f

Online Survey of Feedback

Device Feedback

3. Rate the physical COMFORT of each handgrip device. *
   - Zona Device

4. Rate your ENJOYMENT using each of the handgrip devices. *
   - LabChart Device

Device Net Promoter Score

5. How likely would you be to recommend the LabChart device to a friend/colleague? *
   - Not likely at all

6. How likely would you be to recommend the ZONA device to a friend/colleague? *
   - Not likely at all

7. What would be your suggestion(s) for the optimal handgrip DEVICE?
   - If you do not have a suggestion, please type "n/a". *
Protocol Feedback

Reminder: The Zona Protocol took 11 minutes and it was a series of 4 x (2 min squeeze with 1 min rest). Working at 30% max strength.
Reminder: The LabChart Protocol took 5 minutes and it was a series of 30 x (1 sec squeeze with 5 sec rest). Working at 100% max strength.

8. Rate your ENJOYMENT using each of the handgrip protocols.*

<table>
<thead>
<tr>
<th>To Enjoyment</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
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</thead>
<tbody>
<tr>
<td>Zona Protocol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

9. Rate the EASE of using each of the handgrip protocols *

<table>
<thead>
<tr>
<th>Very Difficult</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>LabChart Protocol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

10. Rate your FATIGUE using each of the handgrip protocols *

<table>
<thead>
<tr>
<th>Not at all Fatiguing</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zona Protocol</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Protocol Net Promoter Score

Reminder: The Zona Protocol took 11 minutes and it was a series of 4 x (2 min squeeze with 1 min rest). Working at 30% max strength.
Reminder: The LabChart Protocol took 5 minutes and it was a series of 30 x (1 sec squeeze with 5 sec rest). Working at 100% max strength.

11. How likely would you be to recommend the Zona protocol to a friend/colleague? *

<table>
<thead>
<tr>
<th>Not likely at all</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
</table>

12. How likely would you be to recommend the LabChart protocol to a friend/colleague? *

<table>
<thead>
<tr>
<th>Extremely likely</th>
<th>10</th>
<th>9</th>
<th>8</th>
<th>7</th>
<th>6</th>
<th>5</th>
<th>4</th>
<th>3</th>
<th>2</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not likely at all</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX 2g

Focus Group Feedback Form

Please provide feedback regarding Mock-SIHG Tool #1

Rate the colour:
0 1 2 3 4 5 6 7 8 9 10
The Worst Very Bad Bad Neither Bad or Good Good Very Good The Best

Comment(s):

Rate the shape:
0 1 2 3 4 5 6 7 8 9 10
The Worst Very Bad Bad Neither Bad or Good Good Very Good The Best

Comment(s):

Rate the size:
0 1 2 3 4 5 6 7 8 9 10
The Worst Very Bad Bad Neither Bad or Good Good Very Good The Best

Comment(s):

Rate the foam grip:
0 1 2 3 4 5 6 7 8 9 10

Comment(s):

How likely would you be to recommend Mock-SIHG Tool #1 to a friend? (check one)
-1 -2 -3 -4 -5 -6 -7 -8 -9 -10
Not At All Likely Very Likely
APPENDIX 2h

Questionnaire of Exercise Barriers

UNIVERSITY OF TORONTO
Faculty of Kinesiology and Physical Education

Long-term Impact of Handgrip Exercise, a pilot study

1. Please comment on what factors promoted / helped / facilitated / encouraged your participation in handgrip exercise?

2. Please comment on what factors inhibited / hindered / discouraged your participation in handgrip exercise?

3. Do you think that handgrip exercise you did improved your ... (circle one)
   
   a) grip strength? Yes  No  I don't know
   b) upper body strength? Yes  No  I don't know
   c) lower body strength? Yes  No  I don't know
   d) blood pressure? Yes  No  I don't know
   e) cholesterol? Yes  No  I don't know
   f) risk of osteoporosis? Yes  No  I don't know
   g) blood vessel health? Yes  No  I don't know
   h) cardiovascular health? Yes  No  I don't know
   i) general health? Yes  No  I don't know
   j) quality of life? Yes  No  I don't know
   k) life expectancy? Yes  No  I don't know
   l) risk of cardiovascular disease Yes  No  I don't know

Thank you 😊
APPENDIX 2i

Physical Activity Enjoyment Scale

<table>
<thead>
<tr>
<th>Physical Activity Enjoyment Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;I enjoy it&quot;</td>
</tr>
<tr>
<td>I feel bored</td>
</tr>
<tr>
<td>I dislike it</td>
</tr>
<tr>
<td>&quot;I find it pleasurable&quot;</td>
</tr>
<tr>
<td>&quot;I am very absorbed in this activity&quot;</td>
</tr>
<tr>
<td>It's no fun at all</td>
</tr>
<tr>
<td>&quot;I find it energizing&quot;</td>
</tr>
<tr>
<td>It makes me depressed</td>
</tr>
<tr>
<td>&quot;It's very pleasant&quot;</td>
</tr>
<tr>
<td>&quot;I feel good physically while doing it&quot;</td>
</tr>
<tr>
<td>&quot;It's very invigorating&quot;</td>
</tr>
<tr>
<td>I am very frustrated by it</td>
</tr>
<tr>
<td>&quot;It's very gratifying&quot;</td>
</tr>
<tr>
<td>&quot;It's very exhilarating&quot;</td>
</tr>
<tr>
<td>It's not at all stimulating</td>
</tr>
</tbody>
</table>
APPENDIX 3a

Chapter 3 Consent

Acute Alterations in Blood Pressure and Potential Mechanisms Following Handgrip Exercise

Principle Investigator:
Danielle Bentley, PhD Candidate, Department of Exercise Science, University of Toronto

Supervisor:
Dr. Scott Thomas, Department of Exercise Science, University of Toronto

Background Information
As researchers, we aim to understand the overall function of the vessels inside the human body following certain stimuli, such as exercise. Following aerobic exercise we know that blood pressure momentarily drops, this is called post-exercise hypotension. It is unclear whether or not the same physiological response will follow isometric handgrip exercise.

Purpose
The purpose of this research project is to determine if post-exercise hypotension results following handgrip exercise. We are studying four different exercise protocols to determine if a varying response occurs.

Procedures
Your full participation in the study will require you to complete five visits to the Human Health and Performance Laboratory within a time-span of two weeks. All sessions will be completed within the Athletic Centre where there is both meter parking and TTC access within walking distance. For each of the sessions you will be required to complete a 4hr fast, a 4hr abstinence from caffeine and a 24hr abstinence from alcohol and strenuous exercise. All sessions will be approximately 90 to 120 minutes in length. The total time spent within the lab upon full study completion will be approximately 9 hours.

The first session will be to collect the necessary preliminary information including the completion of forms, height and weight, and resting blood pressure. In this first session you will also be introduced to the measurement techniques of blood pressure, handgrip exercise, arterial function, venous function, the cold presser test, and the serial subtraction test.

The second session will be for baseline measurement data acquisition. This includes resting blood pressure, arterial function, venous function, cold presser, and serial subtraction.

The remaining three sessions will be for experimental data acquisition. They will be sequenced as follows: seated rest, pre-exercise blood pressure, handgrip exercise (or a seated control), post-exercise blood pressure, arterial function, and venous function. All measurements made during the data collection periods are non-invasive.

Risks and Benefits
All of the tests at the University of Toronto are routinely performed and are associated with minimal risk. There are no known risks associated with the non-invasive measurements involved in this study.

You will not directly benefit from completion of the research project. All travel expenses (up to $30.00) will be fully compensated (inclusive of parking and TTC transit, with original receipts). In addition, you will have the option of selecting either one three-month gym membership to the Athletic Centre ($234.00...
value) or one gift card ($50 value). The gym membership or gift card will be distributed at the end of study completion.

Access to Information, Confidentiality, and Publication of Results
Your personal information, including the results of the above tests will be kept strictly confidential. All results will be coded with a study ID number. The document connecting your name to your identification number will be kept in a locked filing cabinet in the primary investigator’s office. All study data inputted into a computer will be password protected and access will be limited to study investigators only. It is intended that the results of this research project will be publically shared through formal academic presentation and/or publication. In addition, a summary of the research findings will be prepared and shared with you as a research participant.

Voluntary Participation
Your participation in this study is completely voluntary. Your decision to participate in this study (or not), will in no way affect your membership or status (if applicable) at the University of Toronto. Similarly, you are free to withdraw from the study at anytime throughout your enrollment. However, once you have completed the study you will be unable to remove you data. Please note that if you do not fully complete the study you will not be eligible for the compensation of the gym membership or the gift card.

Contacts and Questions
If you have any questions please contact the primary investigator: Danielle Bentley, phone: 416-978-0762, email: danielle.bentley@utoronto.ca

If you have any questions about your rights and/or how you have been treated as a research participant, please contact the Office of Research Ethics at ethics.review@utoronto.ca 416-946-3273.

I, ________________________________, agree to participate in this study, conducted at the University of Toronto, which will provide knowledge about the blood pressure response to handgrip exercise. I understand the above information and have had an opportunity to discuss any questions or concerns with the primary and/or co-investigator. As a participant in this study I will receive a copy of this signed informed consent form. As a participant I understand that the investigators will be available throughout this study to answer any questions that may arise.

I voluntary consent to participate in this study.

Participant’s signature: ______________________________ Date: __________________

Witness name (print): ______________________________ Date: __________________

Witness’ signature: ______________________________
APPENDIX 3b

Chapter 4 Consent

Acute Alterations in Blood Pressure and Potential Mechanisms Following Handgrip Exercise - Follow Up Handgrip Device Feedback -

Principle Investigator:
Danielle Bentley, PhD Candidate, Department of Exercise Science, University of Toronto

Supervisor:
Dr. Scott Thomas, Department of Exercise Science, University of Toronto

Background Information
As researchers, we aim to understand the overall function of the vessels inside the human body following certain stimuli, such as exercise. Following aerobic exercise, we know that blood pressure momentarily drops; this is called post-exercise hypotension. It is unclear whether or not the same physiological response will follow isometric handgrip exercise.
In assessing handgrip exercise, we asked for feedback about the tools we used. We have taken that feedback and created four different handgrip tools (called Mock-SIGH tools).

Purpose
To collect user-feedback on four different Mock-SIGH tools.

Procedures
Your full participation in the feedback session requires that you interact with the four Mock-SIHG tools and completed the provided feedback form. The feedback form will ask you to rate (using a scale) components of the tools. You will also have the opportunity to provide open-ended feedback through the comment boxes on the feedback form.

Risks and Benefits
There are no known risks associated with your participation in these feedback sessions. You will not directly benefit from your participation in these feedback sessions. Your travel for the day will be compensated (1.5hr parking (with receipt) or 2 TTC tokens). As a small token of appreciation, you will receive a $5.00 gift card to Tim Hortons or Starbucks.

Access to Information, Confidentiality, and Publication of Results
Your personal information, including your feedback, will be kept strictly confidential. All results will be coded with a study ID number. The document connecting your name to your identification number will be kept in a locked filing cabinet in the primary investigator’s office. All study data inputted into a computer will be password protected and access will be limited to study investigators only.
It is intended that the results of this research project will be publically shared through formal academic presentation and/or publication. In addition, a summary of the research findings will be prepared and shared with you as a research participant.
Voluntary Participation
Your participation in this study is completely voluntary. You are free to withdraw from the study at any time throughout your enrollment. However, once you have completed the study, you will be unable to remove your data. Please note that if you do not fully complete the study, you will not be eligible for the travel compensation or gift card.

Contacts and Questions
If you have any questions, please contact the primary investigator: Danielle Bentley, phone: 416-978-0762, email: danielle.bentley@mail.utoronto.ca

If you have any questions about your rights and/or how you have been treated as a research participant, please contact the Office of Research Ethics at ethics.review@utoronto.ca or 416-946-3273.

I, ________________________________ (please print), agree to participate in this study by providing feedback on Mock-SIHG tools conducted at the University of Toronto. I understand the above information and have had an opportunity to discuss any questions or concerns with the primary and/or co-investigator. As a participant in this study, I will receive a copy of this signed informed consent form. As a participant I understand that the investigators will be available throughout this study to answer any questions that may arise.

I voluntarily consent to participate in this study.

Participant’s signature: ________________________________ Date: ________________

Witness name (print): ________________________________ Date: ________________

Witness signature: ________________________________
APPENDIX 3c

Chapter 5 and 6 Consent

Long-term Impact of Handgrip Exercise, a pilot study

Principle Investigator:
Danielle Bentley, PhD Candidate, Department of Exercise Science, University of Toronto

Supervisor:
Dr. Scott Thomas, Department of Exercise Science, University of Toronto

Background Information
As researchers, we aim to understand the overall impact of a novel handgrip exercise tool. The effectiveness of expensive clinical tools is already known. It is unclear whether or not the same effectiveness exists with this new tool.

Purpose
Therefore, the purpose of this research project is to determine if the novel handgrip exercise tool is effective.

Procedures
Your full participation in the study will require you to complete four visits to the Human Health and Performance Laboratory within a time-span of eight weeks. In addition, you will complete at-home handgrip exercise 4 times a week for a total of 8 weeks. The in-lab and at-home components are further explained separately.

In-Laboratory
Each of the four laboratory visits will be completed within the Athletic Centre where there is both meter parking and TTC access within walking distance. For each of the sessions you will be required to complete a 4hr fast, a 4hr abstinence from caffeine and a 24hr abstinence from alcohol and strenuous exercise. All sessions will be approximately 90 to 120 minutes in length. The total time spent within the lab upon full study completion will be at maximum 9 hours. The first session will be to collect the necessary preliminary information including the completion of forms, height and weight, and resting blood pressure. In this first session you will also be introduced to the measurement techniques of blood pressure, handgrip exercise, and arterial function. The second session will be for baseline measurement data acquisition. This includes resting blood pressure, handgrip exercise, and arterial function. After this second session you will receive a take-home handgrip tool and you will begin your at-home handgrip exercise regimen.

At the half-way point (at 4 weeks) you will return to the laboratory for a half way assessment of blood pressure, handgrip exercise, and arterial function. Finally, at the end of your 8 weeks you will return to the laboratory for a final assessment of blood pressure, handgrip exercise, and arterial function. All measurements made during the data collection periods are non-invasive.

At-Home
Your at-home training will consist of handgrip exercise that will take you 5 minutes to complete. You are required to complete this 5 minute exercise bout 4/week. You will be instructed on how to use the online exercise adherence program to track your progress. The exercise is meant to be easy and fun!
Risks and Benefits
All of the tests at the University of Toronto are routinely performed and are associated with minimal risk. There are no known risks associated with the non-invasive measurements involved in this study. You will not directly benefit from completion of the research project. To help compensate you for your travel and your time you receive a one-time cash payment of $100.00 upon completion of your final visit. In addition, to express our gratitude you will have the option of selecting either a two-month gym membership to the Athletic Centre ($156.00 value) or a gift card ($50 value). All compensation will be distributed at the end of study completion.

Access to Information, Confidentiality, and Publication of Results
Your personal information, including the results of the above tests will be kept strictly confidential. All results will be coded with a study ID number. The document connecting your name to your identification number will be kept in a locked filing cabinet in the primary investigator’s office. All study data inputted into a computer will be password protected and access will be limited to study investigators only. It is intended that the results of this research project will be publically shared through formal academic presentation and/or publication. In addition, a summary of the research findings will be prepared and shared with you as a research participant.

Voluntary Participation
Your participation in this study is completely voluntary. Your decision to participate in this study (or not), will in no way affect your membership or status (if applicable) at the University of Toronto. Similarly, you are free to withdraw from the study at any time throughout your enrollment. However, once you have completed the study you will be unable to remove your data. Please note that if you do not fully complete the study you will not be eligible for the compensation.

Contacts and Questions
If you have any questions please contact the primary investigator: Danielle Bentley, phone: 416-978-0762, email: danielle.bentley@mail.utoronto.ca
If you have any questions about your rights and/or how you have been treated as a research participant, please contact the Office of Research Ethics at ethics.review@utoronto.ca 416-946-3273.

I, _________________________________, agree to participate in this study, conducted at the University of Toronto, which will provide knowledge about the blood pressure response to handgrip exercise. I understand the above information and have had an opportunity to discuss any questions or concerns with the primary and/or co-investigator. As a participant in this study I will receive a copy of this signed informed consent form. As a participant I understand that the investigators will be available throughout this study to answer any questions that may arise.

I voluntary consent to participate in this study.

Participant’s signature: ____________________________ Date: ____________________

Witness name (print): _______________________________ Date: ____________________

Witness’ signature: ________________________________
APPENDIX 4a

Reliability Study – Published Abstract

The Influence of Sex on Non-invasive Assessments of Vascular Health in Young Healthy Participants

Danielle C. Bentley¹, Scott C. Thomas¹

¹Department of Exercise Sciences, Faculty of Kinesiology and Physical Education, University of Toronto.

Non-invasive instruments and procedures used for the assessment of arterial and venous health are ideal because they permit repeated assessments throughout exercise intervention studies. Arterial health and venous health are commonly estimated using applanation tonometry and venous function, respectively. Few studies have reported the relationship between these measures of vascular health. We assessed the reproducibility (ICC) and correlation (Pearson r) of Augmentation Index and Venous Compliance in a sample men (n=15) and women (n=10). Together, participants were healthy (SBP/DBP: 104.1±7.3 / 68.3±5.0mmHg, HR: 63.7±7.9bpm), young (Age: 24.7±3.2 years), and physically active (Rapid Assessment of Physical Activity: 6.2±1.0). All participants completed an initial familiarization session, followed by two identical experimental sessions where both arterial Augmentation Index (AIx) and Venous Compliance (dV/dP) were measured. AIx values were accepted only if an operator index > 90%. Reliability between days for AIx was extremely high (ICC: 0.95, p < 0.000) while dV/dP scores at 20mmHg were less reliable (ICC: 0.83, p < 0.000). There was a negative correlation between intra-individual same day AIx and dV/dP variables (r = -.56, p <0.01). There was a significant influence of sex such that males had lower AIx values (Mean± SEM) (0.17±2.50) than females (15.27±2.65) (p<0.000), and lower dV/dP values (0.10±1.25) than females (8.41±1.20) (p<0.000). Based on these results, studies of vascular health should consider the arterial distensibility measurement of AIx and the venous function measurement of dV/dP as independent reliable variables that vary greatly between the sexes.

Abstract Sponsor: (Dr. Scott Thomas, University of Toronto)

Corresponding Author: Danielle Bentley, Department of Exercise Sciences, Faculty of Kinesiology and Physical Education, University of Toronto, Toronto Ontario Canada. danielle.bentley@mail.utoronto.ca

Funding: CIHR Banting and Best CGS Doctoral Research Award

Applied Physiology, Nutrition, and Metabolism 39:S3
The Influence of Sex on Non-invasive Assessments of Vascular Health in Young Healthy Participants

Danielle E. Bentley & Scott G. Thomas
Faculty of Kinesiology and Physical Education, University of Toronto, Toronto, Ontario

Background
- In the exercise sciences, it is common to assess a participant’s vascular health before and after an intervention study.
- This assessment can be completed non-invasively.

Various health can be measured using an Augmentation Index (AIx), a non-invasive measurement of arterial distensibility. It is unclear how reliable these measurements are when performed by the same researcher.

Various health can be measured using Venous Plethysmography (DVIP); a non-invasive measurement of venous compliance is unclear if one’s arterial distensibility (AIx) and venous compliance (DVIP) correlates.

Purpose
- To determine the test-retest reproducibility of both AIx and DVIP in men and women.
- To determine the intra-individual correlation between AIx and DVIP in men and women.

Methods
- Participants completed a 4x4 within-subjects design with caffeine, 24-hour abstinence from alcohol and strenuous activity.

Initial Study Visit 1
- All three visits were identical.
- 10 minutes of seated rest (resting BP and HR).
- Transitions to supine (5 minutes).
- Arterial Distensibility (AIx), 5 minute rest.
- Venous Compliance (DVIP), 5 minute rest.
- Test-retest reliability of AIx and DVIP was assessed using intraclass correlation coefficient.

Intra-individual correlation between AIx and DVIP was assessed using Pearson r.

Results
- Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Men (n=15)</th>
<th>Women (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>24.9 ± 3.5</td>
<td>23.6 ± 3.4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.8 ± 3.2</td>
<td>23.9 ± 3.3</td>
</tr>
<tr>
<td>Grip Strength (kg)</td>
<td>28.4 ± 7.6</td>
<td>8.7 ± 3.7</td>
</tr>
<tr>
<td>Forearm Girth (inches)</td>
<td>11.0 ± 0.8</td>
<td>9.3 ± 0.7</td>
</tr>
<tr>
<td>Resting SBP (mmHg)</td>
<td>109.9 ± 6.1</td>
<td>100.1 ± 5.7</td>
</tr>
<tr>
<td>Resting DBP (mmHg)</td>
<td>69.3 ± 5.6</td>
<td>68.3 ± 3.0</td>
</tr>
</tbody>
</table>

- There was a significant correlation between arterial distensibility data on visit day 1 versus visit day 2, ICC = 0.90, p = 0.001, Bland-Altman plot shown below.

- There was a significant correlation between venous compliance data on visit day 1 versus visit day 2, ICC = 0.70, p = 0.001, Bland-Altman plot shown below.

Results (cont.)
- There was an insignificant correlation between paired data for arterial distensibility and venous compliance, among both men (r = 0.11, p = 0.57) and women (r = 0.08, p = 0.70).

- Venous Compliance (DVIP) was shown below.

Interpretation
- Independently, arterial distensibility and venous compliance are both highly reliable, non-invasive measurements of vascular health.
- As expected, augmentation index was significantly affected by age. As shown in the male participants, younger males had lower AIx (M = 4.12, SD = 2.50) than older males (M = 5.8, SD = 2.0, t(12) = 2.90, p = 0.007).
- Current AIx values align with population mean values of 4.67 (20y) and 3.83 (50y) [AIxCOR, 2013].
- Based on measures of AIx and DVIP in the resting state, arterial health and venous health are independent of each other in young healthy men and women.
- This mirrors the differing impact of exercise stimuli on the vasculature.
- Following an acute bout of handgrip exertion, AIx increases by ~10% [Cawson et al., 2009].
- Whereas habitual resistance training increases forearm venous compliance by ~16% [Kawano et al., 2010].
- The impact of various exercise stimuli stimuli (dynamic and isometric) on arterial and venous health should be assessed using both AIx and DVIP.
- Adaptation of both components to short- and long-term exercise should be independently evaluated.

APPENDIX 5

Integrated Knowledge Translation Results

Knowledge users (KUs) (i.e. researchers, clinicians) were invited to complete an online survey designed to acquire opinions surrounding handgrip exercise. The primary goal of this survey was to determine what the most (and least) important research outcomes were from the point of view of KUs. By doing so, I was able to ensure that my research would be clinically useful and highly transferable.

Invitations to complete the survey were sent via email to sample of convenience. Although more than twenty KUs attempted to complete the survey online, only seven were able to complete every component. This is likely due to incompatible user interface on smartphones. Participants self-identified as clinicians (n=3), a physician (n=1), kinesiologists (n=3), cardiac rehabilitation specialists (n=4) and an academic (n=1) with a range of experience from <5 years (n=2) to > 15 years (n=3) and in between (n=2).

None of the survey respondents were currently using HG exercise strategies in their daily practices. Furthermore, two KUs had never even heard of it and five KUs believed that the area required more structured and dedicated research.

“Almost all of my patients attend a cardiac rehab program where they participate in regular aerobic and resistance training. I am unclear if [handgrip] adds incremental benefit over the usual [cardiac rehabilitation] exercise program. If yes, then I would be sure to add it as an additional exercise.”

Specific survey questions were directed towards the usefulness of collecting particular outcome variables. This information was especially useful in informing my overall dissertation research design. Participants were asked if they believe the acquisition of data pertaining to a variety of variables was useful (yes/no response). I was interested in segregating the during-exercise time point from the post-exercise time point. The results of those questions have been summarized in chart form below.

<table>
<thead>
<tr>
<th>Variable</th>
<th>During an Exercise Bout</th>
<th>Following Exercise Cessation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Systolic Blood Pressure Variability</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Diastolic Blood Pressure Variability</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Heart Rate Variability</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Participant Enjoyment</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Ratings of Perceived Exertion (RPEs)</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Exercise Protocol Feedback</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
There were two important take away messages from this work. First and foremost, my original research designs did not include assessments of participant use (RPEs, feedback, enjoyment, etc.). This survey provided me with the knowledge that KUs are interested in knowing about the opinions of exercise participants. As a result, the Short-Term Study (Chapter 3) and the Long-Term Training Study (Chapter 5) were redesigned to include these opinion-based assessments.

Second, it was very interesting to see that few KUs displayed a strong interest in obtaining mechanistic information of vascular perturbations. There was less consistent interest in measures of arterial or venous structure/function. Given that this research was designed with these original research outcomes of interest (as determined the research advisory committee) the vascular assessments remained with the design.

The integration of KU feedback is a unique strength of this thesis. Moving forward with future work, it is imperative that KU feedback and opinions be fully integrated into the conceptualization phase of research programs. Not only does this feedback reveal previously unknown research interests, but it ensure that the creation of knowledge is clinical relevant and useful.
APPENDIX 6

Submitted Systematic Review Protocol

Resting blood pressure reductions following handgrip exercise training and the impact of age and sex: protocol for a systematic review

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Abstract

Background: The risk of developing cardiovascular disease (CVD) is directly correlated to one’s resting blood pressure (BP), age and, biological sex. As such, maintaining BP at an optimal level is critical as we strive to reduce the global burden of CVDs. Maintenance of optimal resting BP can often be accomplished with regular exercise (ie. handgrip exercise); a non-pharmaceutical, easy to follow, low-cost strategy.

Methods/design: A systematic search of the literature will be conducted for experimental studies that report the impact of handgrip exercise training on resting systolic blood pressure. The databases Medline, Embase, Cochrane Reviews, Cumulative Index to Nursing and Allied Health Literature (CINAHL), SPORTDiscus, Web of Science, the Allied and Contemporary Medicine (AMED), PubMed, and Scopus will be search until 1 June 2015. Screening of potential articles, data abstraction, and quality appraisal will be completed in duplicate independently. Methodological quality will be determined using the Quality Assessment Framework developed by the Cochrane Collaboration and the Newcastle-Ottawa Quality Assessment Scale as appropriate. Any discrepancies will be resolved by a third author. Findings will be constructed in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.

Discussion: This systematic review will determine the overall effectiveness of handgrip exercise training in improving various cardiovascular variables, such as resting blood pressure. A focused assessment will contrast effectiveness in men compared to women and young compared to old study participants. This information is essential to consolidate before moving forward with the development and implementation
of handgrip exercise training programs which are designed to best meet the needs of particular cohort, such as aged women.

**Systematic review registration:** PROSPERO CRD42015019792

**Keywords:** Isometric exercise, Handgrip exercise, Blood Pressure, Aging, Women's health, Cardiovascular risk

**Background**

**Rationale**
Cardiovascular disease (CVD) is the number one cause of death worldwide, representing nearly one-third (31%) of global deaths in 2012 [1]. There is a strong, independent correlation between CVD morbidity and mortality, and high blood pressure (BP) [2], with more than 50% of all CV diseases directly related to high BP [1]. Therefore, maintaining BP at an optimal level is critical in order to reduce the global burden of CVD [3].

In addition to the direct impact of high resting BP, the risk of developing CVD is also influenced by both an individual’s age and their biological sex. Although women will present with CVD 10 years later than men, a trend that is typically attributed to men presenting with greater risk factors in early age [4], the exponential nature of the increase in CVD around the age of 55–60 years in women suggests menopause augments CVD risk [5].

The disparity in CVD incidence between aged men and women is now recognized worldwide, with the American Heart Association publishing separate guidelines for CVD prevention for men and women [6,7,8] and the European Society of Cardiology formally publishing public policy documents [9]. Among Canadian women specifically, the relative-risk of developing CVD increases fourfold after the menopause transition [10], a statistic that highlights the impactful interaction of age and biological sex.

Maintenance of optimal resting BP can often be accomplished with regular exercise; a non-pharmaceutical, easy to follow, low-cost strategy. It is recommended that individuals with above optimal BP engage in non-pharmaceutical interventions, such as exercise training, to control BP and ultimately reduce CVD risk [11]. Although regular aerobic exercise (ie. jogging, cycling, etc.) consistently reduces resting BP (-3.5 /-2.5 mmHg) [12], barriers such as lack of exercise self-efficacy, physical limitations, and financial obstacles can limit uptake. An alternative to traditional aerobic exercise is isometric handgrip (IHG) exercise, which is easily accessible, requires little time, and may serve to introduce exercise behaviours to reluctant individuals. Recently, Carlson and colleagues (2014) systematically reviewed the isometric resistive exercise literature, identified nine studies that met rigorous research design criteria (eg. Randomized Clinical Trial, duration >4 weeks), and reported a significant reduction in resting BP (mean: Confidence Interval: Systolic –6.77: –7.93 to –5.62mmHg; Diastolic –3.94: –4.73 to –3.16 mmHg). However, the small number of included studies precluded assessing the potential impact of age or sex on the outcomes [13]. Prior to this, reviews of isometric exercise literature have consistently observed significant BP reductions with both similarly restrictive eligibility [14] as well as less restrictive criteria [2]. However, the potential influence of participant age and biological sex has yet to be determined and categorized with appropriate sub-analyses.

**Review Objectives**
Based on the currently available review data of handgrip exercise, there is a need to update the systematic review literature, using a broad set of eligibility criteria and an inclusive search strategy. Furthermore, there is an opportunity to assess the potential impacts of age and sex on the effectiveness of handgrip exercise training in improving various cardiovascular variables, such as resting BP.
This review will be the first to identify and segregate the potential influence of participants’ age and sex, as well as the interaction of these two defining categories. We are especially interested in segregating and describing the main effects of handgrip exercise training for the specific cohort of post-menopausal women. Together, this information will be instrumental in providing rationale for the development and implementation of IHG training programs which are designed to best meet the needs of particular cohorts, such as aged women.

Methods/Design
The proposed systematic review conforms to the preferred reporting items for systematic review and meta-analysis protocol (PRISMA-P) guidelines [15]. In accordance with the PRISMA-P guidelines, this systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 23 June 2015 (registration number CRD42015019792).

Eligibility Criteria
Types of studies
The inclusion criteria have been designed to be purposefully broad. We will include prospective research designs classified as RCTs, RCTs with a crossover design, experimental exercise interventions without a designated control group, or pilot studies. We will exclude retrospective designs, case series, and case reports.

Participants
We will include studies that recruit adult humans ≥18 years of age. We will categorize participants as being ‘younger’ (= <55 years) or ‘older’ (= >55yrs). If necessary, authors of studies with participant’s ages across our categories will be contacted directly in order to facilitate the segregation of results based on age. It is anticipated that participants may have various comorbidities (ie. hypertension, heart failure, diabetes, etc.) with an assortment of medication use. All comorbidities and medications will be numerically coded accordingly. We will include studies that recruit men, women, or mixed samples and will categorize participants based on biological sex. If necessary, authors of mixed-sex studies will be contacted directly in order to facilitate the segregation of results based on sex.

Interventions
Of interest are interventions that use at least four weeks of handgrip exercise as a training modality and measure resting and/or ambulatory systolic BP before and after the training program. It is anticipated that handgrip exercise interventions will vary in range of prescribed grip intensities, length of each individual isometric hold, frequency of handgrip use, etc. All training details will be captured in the data abstraction with the overall training stimulus quantified using a calculation of effort using a Time (in seconds) x Tension (in percent of maximal volitional contraction) Product, such that TTP = Time (sec) x Tension (%MVC).

Comparators
We anticipate that a small proportion of included studies will use a defined control group. As such, we are planning to use the within study pre- to post-intervention change scores as the assessment of training effectiveness for all cardiovascular variables. Additional post-hoc assessments will be completed including an analysis of the impact of age (younger versus older) and the impact of sex (women versus men).

Outcomes
Eligible studies will be those that look at the impact of handgrip exercise training on resting systolic BP. Studies which do not assess a pre- to post-intervention change score will be deemed ineligible. This change in BP may be a primary outcome of the included studies, or a secondary/tertiary outcome. Included studies may also assess (as a primary, secondary, or tertiary outcome) the impact of handgrip training on a variety of additional cardiovascular assessments.

Timing
Studies will be eligible for inclusion only if the training intervention is at least four weeks in duration. A list of excluded publications with interventions <4 weeks in duration will be provided as an appendix.
Setting
Eligibility will not be restricted to specific exercise settings. Exercise training may occur in a controlled laboratory, at the participant’s home, in a group training environment, or as a combination of settings.

Language
We will include articles reported in the English, Portuguese, and French languages. A list of possibly relevant titles in other languages will be provided as an appendix.

Information Sources
We will perform a systematic, computer-assisted, literature search of existing evidence using the online databases of Medline, Embase, Cochrane Reviews, Cumulative Index to Nursing and Allied Health Literature (CINAHL), SPORTDiscus, Web of Science, the Allied and Contemporary Medicine (AMED), PubMed, and Scopus. To ensure literature saturation, reference lists from both published relevant reviews as well as retrieved articles will be hand-searched and additional papers assessed for eligibility. We anticipate having to contact corresponding researchers in order to adequately segregate published results for our desired sub-analyses on age (younger versus older) and sex (women versus men).

Search Strategy
No study design, date, or language limits will be imposed on the search strategies. When available, search limits were used on the variables of AGE (“adult <18-64” and “aged <65+”) and TYPE (“human”). Relevant studies published up to 1 June 2015 will be retrieved using a specific search strategy created in conjunction with a University of Toronto research librarian with expertise in systematic reviews. The search strategy was kept purposefully broad to increase the opportunity to identify potentially relevant papers. A representative OVID keyword search transcript is presented here which will be applied to the databases of Medline, Embase, and AMED.
2. [training] OR [intervention*] OR [exercise*] OR [physical activity]
3. [blood pressure] OR [systolic] OR [cardiovascular]

Study Records
Data Management
Using the aforementioned search strategy, titles and abstracts from identified articles will be imported into EndNote (Version 5.0 Thompson Reuters, 2011), an electronic reference management software. Extracted data from eligible studies will be entered into a custom-made abstraction framework in Microsoft Excel (version 12.3.6, Microsoft Corporation, 2007) and analyzed using SPSS (version 22, IBM SPSS Statistics, 2015).

Selection Process
Following duplicate removal, the entire list of identified articles will be independently screened by DB and CN, with discrepancies assessed for a third time by ST. Overall, the screening process will include titles and abstracts of potentially relevant articles to appraise eligibility using the custom-made screening form. Eligible articles will be those that study the direct impact of ≥ 4 weeks of handgrip exercise training on measures of cardiovascular health within a cohort of adult humans. Those articles which do not meet the eligibility criteria will be excluded. References lists of retrieved articles and published relevant reviews will be hand-searched for additional papers and assessed for eligibility. Full texts of all studies meeting the inclusion criteria will be retrieved and printed for detailed review, data abstraction, and subsequent analysis using a custom-made abstraction framework.

Data Collection Process
Data abstraction from all included articles will be independently completed by DB and CN with discrepancies assessed by ST. A custom-made data abstraction framework will be used to record significant study characteristics. Amendments to the abstraction framework and corresponding data extraction variables will be made upon review of included articles, if necessary. When required,
corresponding authors will be contacted directly to obtain necessary additional information. It is possible that the same data from a single study may be presented in multiple reports. In order to avoid this, studies with at least one shared author will have participant details directly compared to assess potential duplication of results.

**Data Items**

It is anticipated that a diverse range of research methodology will be identified within this review, and hence a statistical meta-analysis is unlikely to be appropriate. We will extract information regarding study design details (ie. year of publication, exercise prescription, bilateral or unilateral exercise, time-tension product of handgrip protocol, etc.), participant details (ie. age (segregate for younger and older), sex (segregate for male and female), resting BP status, medication use, co-morbidities, etc.), primary cardiovascular variables (ie. impact of handgrip training on blood pressure, heart rate, arterial health and function measurements, venous health and function measurements, etc.), and any exercise training adherence information (ie. number of drop-outs, compliance to exercise protocol, etc.).

We will make the assumption that women in our “older” age category (≥55yrs) will be post-menopausal. Although natural menopause in women can be affected by a variety of factors such as ethnicity, diet, physical activity, and genetics (Gold, 2011), the National Institute of Aging states that the most recent average age of menopause is 51 (NIA, 2013).

**Outcomes and Prioritisation**

Our primary outcome of interest will be:
- change in systolic BP as a result of handgrip exercise training. Systolic BP can be measured as resting or ambulatory. Studies which do not report change in systolic BP over time will be excluded.

Secondary outcomes of interest will be collected and analyzed if sufficiently reported. They will be:
- change in resting diastolic blood pressure
- change in heart rate
- change in arterial health and function (ie. pulse wave velocity, arterial distensibility, reactive hyperaemic forearm blood flow, flow mediated vasodilation)
- change in venous health and function (ie. venous compliance).
- change in autonomic nervous system indicators (ie. MSNA, heart rate variability, blood pressure variability, and CV reactivity)

For all included outcomes we will segregate out the impact of age (younger versus older) and sex (women versus men).

**Assessment of Study Quality**

It is anticipated that included studies will be of various research designs some with and some without a randomized control group. Therefore we will utilize two corresponding assessment tools. For randomized controlled trials we will use the Quality Assessment Framework developed by the Cochrane Collaboration to assess the following sources of bias: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants/personnel and other potential threats to validity), attrition bias (incomplete outcome data), detection bias (blinding of outcome assessment), and reporting bias (selective outcome reporting) [18]. For experimental exercise interventions without a designated control group, we will use an adapted form of the Newcastle-Ottawa Quality Assessment Scale (NOS) [19].

**Data Synthesis**

Minimum Criteria

Before proceeding with statistical analysis of results, studies which have been identified as having a “high risk of bias” using the aforementioned Cochrane Collaboration risk of bias assessment tool or having less than 4 stars on the NOS star-rating will be removed.
Planned Summary of Measures
Clinical cardiovascular outcomes are measured along standard measurement scales. Therefore, change in these CV outcomes (ie. blood pressure, heart rate, vascular health assessments) will be calculated as weighted mean differences (with a 95% CI). When available, data will be segregated based on the age and the sex of individual participants.

Planned Exploration of Consistency
The heterogeneity of effects will be assessed using both the chi-squared test (an assessment of the presence of heterogeneity) and the I² (an assessment of the impact of heterogeneity).

Subgroup Analysis
Subgroup analyses will be used to explore possible sources of heterogeneity including: (1) participant characteristics such as age, sex, resting BP status at commencement of exercise training, (2) exercise characteristics such as handgrip force prescription, length of training, type of tool used, and (3) location of exercise training such as at-home or in-laboratory.

Planned Synthesis Presentation
The presentation of review results will be constructed in accordance with the PRISMA guidelines.

Strength of the Evidence
The Grading of Recommendations Assessments, Development and Evaluation (GRADE) approach will be used to assess the quality of evidences for all review outcomes across the domains of risk of bias, inconsistency, imprecision, indirectness, publication bias, and factors that increase the confidence in an effect (ie. large effect sizes, dose effect relations).

Discussion
Strengths and Limitations
A strength of this review is the systematic and fully transparent approach that is being taken, which draws on recommended and validated methods [16]. The review is thorough and broad, ensuring that a comprehensive representation of information results. In addition, the use of two separate reviewers for the screening process, data abstraction, and quality appraisal will increase the strength of conclusions.
A potential limitation of this review is the anticipated volume of literature. Although handgrip exercise has been used for decades as a short-term stressor, the use of HG as a training modality is more recent. Therefore, it is anticipated that the majority of published research using handgrip exercise training will have been conducted in the last 5 years due to the focused attention of isolated research groups. As such, this review will include a description of included articles, such as a number of articles published each year, to enhance transparency.
In conclusion, we will perform this systematic review to determine the overall effectiveness of handgrip exercise training in improving various cardiovascular variables, such as resting blood pressure. A focused assessment will contrast effectiveness in men compared to women and young compared to old study participants. This information is essential to consolidate before moving forward with the development and implementation of handgrip exercise training programs which are designed to best meet the needs of particular cohort, such as aged women. In the immediate future, the findings from this review will be useful for exercise researchers and clinicians. It is anticipated that following supplementary primary research, this information will be useful for individuals looking to manage their blood pressure through non-pharmaceutical interventions.

Abbreviations
Competing Interests
There are no competing interests to disclose.

Author Contributions
DCB and SGT conceptualized the idea for this review. DCB, CHN and SGT contributed to the development of the selection criteria, the risk of bias assessment strategy, and the data extraction criteria. DCB is the guarantor and drafted the manuscript. CHN and SGT revised the manuscript. All authors read and approved the final manuscript.