THE ROLE OF ISOMETRIC EXERCISE TRAINING ON REDUCTIONS IN RESTING BLOOD PRESSURE: HUMAN TRIALS AND THE INFLUENCE OF PERIPHERAL VASOACTIVE AND INFLAMMATORY BIOMARKERS

by

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ABSTRACT

BENJAMIN DH. GORDON. Role of Isometric Exercise Training On Reductions in Resting Blood Pressure: Human Trials and the Influence of Peripheral Vasoactive and Inflammatory Biomarkers (Under the direction of DR. REUBEN HOWDEN).

Approximately 1 billion people worldwide and ~87 million adults in the United States alone are affected by hypertension [HTN: high blood pressure (HBP)]. Primary treatment avenues for HBP management include lifestyle modification (e.g. diet, exercise, weight loss, and smoking cessation) and pharmacological therapy. Research has indicated isometric exercise training (IET) is associated with lowering resting blood pressure (RBP). This activity is safe, relatively inexpensive, and easy to perform. While generally effective several factors may influence the degree of responsiveness to IET including age, chronic disease, current pharmacological management, time spent exercising, home-based training, effects of systemic biomarkers, and muscle mass. Therefore the aims of this dissertation were to determine the significance of several contributing factors including time, age, disease, the efficacy of home-based isometric exercise, biomarkers, and muscle mass on reductions in RBP following IET. This work identified the lasting effects of an extended isometric exercise training program (chapter 2), outlines the importance of disease and medications regimen in subject responsiveness to intervention (chapter 3), proposes the positive implications for home-based programming for training dissemination to the greater hypertensive population (chapter 4), and begins to elucidate upon unknown mechanisms contributing to lowered RBP following IET (chapter 5). In chapter 2, I assessed whether or not completing 12 weeks of IET programming can improve high blood pressure measures and sustain positive

outcomes over extended periods of detraining in older recreationally active adults. In chapter 3, I assessed the efficacy of IET in cardiopulmonary rehabilitation patients. In Chapter 4, I evaluated efficacy of home-based training regimens compared to face-to-face lab-based protocols. In chapter 5, I assessed whether or not completing 6-weeks of IET in two different muscle groups influences both RBP and biomarkers of vasoactivity and inflammation acutely and with training. This dissertation will help to disseminate a critical next step, providing an opportunity for effective programming with hopes of characterizing a mechanism contributing to BP reductions induced by IET thus aiding in the fight against HBP both in the lab and in the community.

DEDICATION

To my wife, Em

and

my parents

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LIST OF ABBREVIATIONS

HTN	Hypertension
HBP	High Blood Pressure
WHO	World Health Organization
BP	Blood Pressure
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
RBP	Resting Blood Pressure
HR	Heart Rate
IET	Isometric Exercise Training
IHG	Isometric Handgrip
MVC	Maximal Voluntary Contraction
IBC	Isometric Bicep Curl
ILE	Isometric Leg Extension
BFR	Blood Flow Restriction
RIC	Remote Ischemic Conditioning
PIT	Physiological Ischemia Training
TPR	Total Peripheral Resistance
VEGF	Vascular Endothelial Growth Factor
IL-6	Interleukin-6
TNF-α	Tumor Necrosis Factor Alpha

CHAPTER 1. BACKGROUND & SIGNIFICANCE OF PROPOSED RESEARCH

Introduction

Hypertension (HTN, high blood pressure; >140 and/or >90 mmHg) and its management are critical public health issues, linked to early onset cardiovascular and stroke-related morbidity and mortality [WHO, 2013]. An estimated 1 billion people (~1.5 billion by 2025) worldwide and ~87 million in the United States are affected by HTN [Benjamin et al. 2017]. Furthermore, HTN is estimated to affect nearly half of all US adults (i.e., 46%) costing the US health care system approximately 46 billion dollars per year [Merai et al. 2016, Mozzafarian et al. 2015; Whelton et al. 2017].

HBP is the primary contributing risk factor for advanced cardiovascular disease. Primary disease effects of HBP include but are not limited to coronary artery disease, heart failure, stroke, and chronic kidney disease [Danaei et al. 2009; Murray et al. 2010]. HBP poses both acute and long-term health risks on the pathophysiological development of these conditions [Danaei et al. 2009; Murray et al. 2010;]. Interestingly, beginning as early as the 1960's a decline in mean systolic (SBP, 10%) and mean diastolic (DBP, 13%) in US adults >40 years had been reported. Such a decline, was likely due to significant improvement in diagnosis, awareness, and current methods of BP management [Cutler et al. 2007]. Despite this considerable achievement, the number of individuals diagnosed each year in the United States thereafter with HBP continues to rise and was estimated to be 64-72 million in 2014 [Kovell, 2015; Navvar-Boggan et al. 2014; Nwanko et al 2013;] and is now ~87 million following a 2017 update by the American Heart Association [Benjamin et al. 2017]. A trend of this magnitude underscores the significance of HBP and emphasizes the importance of appropriate or new management strategies to combat the ever-growing public health problem.

The underlying cause of primary or essential HBP is unclear as blood pressure is elevated for no readily definable reason [Brook et al. 2013; Lee, Williams and Lilly, 2011]. Moreover, when described by some medical professionals HBP has been termed a description as opposed to a diagnosis, based upon a patient exhibiting a “physical finding” as a result of no prior cause [Lilly et al. 2011]. For the sake of continuity and simplicity, this dissertation will employ the term ‘diagnosis’ throughout, as it is the most recognized descriptive terminology in the current literature.

The American Heart Association (AHA), World Health Organization (WHO) and American College of Sports Medicine (ACSM) all promote lifestyle modification and early pharmacological management for lowering RBP. Despite supporting evidence adherence rates to aforementioned practices remain low and 2/3 of individuals diagnosed with HBP are still uncontrolled despite heightened awareness [Brook et al. 2013; Germino, 2009].

Alternative strategies to promote not only clinically significant reductions in RBP but enhanced maintenance strategies for long-term BP control within safe limits are now required. Lifestyle modifications alone or coupled with pharmacotherapy are primary treatment and management strategies currently accepted by major health-related organizations to promote substantial improvements in cardiovascular related morbidity and mortality [WHO, CDC, American Heart, and ACSM]. Further sub-categorization of existing strategies includes diet modification (low salt), habitual exercise (150 min), and antihypertensive medications [Brook et al. 2013; Chobanian et al. 2003; Williams et al.

2004; Whelton et al. 2017]. Positive health outcomes with these strategies are well documented; however current trends illustrate that both adherence to exercise programs, disinterest in exercise, cost, and side effects of medications are considerable barriers to successful BP control [Brook et al. 2013; Chobanian et al. 2003; Vawter et al. 2008].

To reiterate, a 2017 update on Heart Disease and Stroke Statistics expresses a continuing trend, showing limited signs of plateauing (72 million in 2014, and 87 million in 2017) [Benjamin et al. 2017]. Thus, novel strategies that are safe, easy to perform, and manageable amidst a busy lifestyle are necessary to promote and maintain a healthy BP to manage disease [Brook et al. 2013; Pimenta and Oparil, 2012]. One such strategy, which has received considerable attention in the last two decades, has been termed isometric exercise training (IET). Isometric muscle contractions and the acute cardiovascular responses (i.e. significant elevations in BP) have been described previously during maximal and whole body skeletal muscle contractions [Rowell, 1993]. However, the first study to identify IET as capable of lowering RBP was observed in 20-35-year-old healthy adults in 1992, utilizing low-moderate intensity handgrip exercise [Wiley, 1992]. Since its inception, IET studies have been conducted utilizing a multitude of exercise modalities and protocols in human subjects [see below for a detailed introduction to IET].

In line with the barriers of successful disease management, what makes IET attractive is that it is considerably effective, simple to do, safe to engage in, and cost effective [Araujo et al. 2011; Goessler et al. 2016; Millar et al. 2008; Olher et al. 2013;]. Furthermore, the time required to elicit significant reductions in RBP and to improve other cardiovascular parameters (e.g. PP and MAP) is minimal, requiring as little as 15-

minutes per day, 3 days per week for 4-10 weeks. In Summary, IET is a potent stimulus for achieving significant reductions in RBP (both systolic and diastolic). Furthermore, given its recent appraisal and recommendation by the American Heart Association and American College of Cardiology, this modality of exercise may be the next prescribed lifestyle intervention to increase adherence, lower cardiopulmonary disease risk and positively impact quality of life [Brook et al. 2013; Whelton et al. 2017].

Notably, while IET has shown to significantly lower RBP in many demographics and all blood pressure classifications little is known regarding protocol variables (e.g. duration, intensity, exercise type) and mechanisms responsible for these adaptations. Two reviews [Lawrence et al. 2014; Millar et al. 2014] including one published from our laboratory, specify important variables likely involved in training adaptations [Lawrence et al. 2014]. Determination of population specific IET responses along with elucidating upon proposed adaptations leading to sustained reductions in RBP will provide insight into potential mechanisms that align with well established adaptations to traditional forms of exercise training; aerobic and resistance modalities.

While it is beyond the scope of this dissertation to examine every aspect of IET and BP, the aim of the proceeding studies (chapters 2, 3, 4 and 5) was to provide a deeper understanding of IET and BP, identifying four principal gaps in the literature that may affect human RBP in response to IET that are not fully understood. Moreover, the outcome of each proceeding chapter builds upon the previous whereby limitations and pitfalls at each stage are identified, addressed and modified accordingly. In brief, these included recruitment and retention of participants, minimizing barriers and improving adherence, and response heterogeneity. With the theme of improved RBP control, this dissertation will have four principal components, (1) at risk demographics, (2) maintenance of RBP adaptations to IET, (3) enhancement of exercise adherence with home-based exercise, and (4) potential mechanisms responsible for RBP adaptations via downstream effects of systemic vasoactive and inflammatory biomarkers, reported to be associated with adaptations to exercise training.

Background and Literature Review

Regulation of Arterial Blood Pressure

Blood pressure (BP) = cardiac output x total peripheral resistance [Joyner et al. 2014; see below for a detailed description of CO and TPR]. Arterial BP is the pressure applied to the luminal surface of arteries extending throughout the entirety of the cardiovascular (CV) system of humans and other mammals [Clifford, 2011; Joyner et al. 2014]. Clinically, arterial BP is represented by both an upper (systolic; SBP) and lower (diastolic; DBP) parameter. As the heart completes a cardiac cycle, SBP coincides with a contraction and emptying phase or systole whereas DBP coincides with a relaxation or filling phase termed diastole [Guyton, 2005]. Moreover, it is well established that BP is the primary variable responsible for central and peripheral cardiovascular homeostasis [Ackermann, 2004; Joyner et al. 2014].

Under normal resting conditions, blood pressure regulatory mechanisms are required to maintain appropriate blood flow to vital organs (e.g., the heart and brain) [Ackermann et al. 2004; Ichinose et al. 2014; Joyner et al. 2014; Raven and Chapleau, 2014; Rowell, 1993]. Regulation of an optimal blood pressure in the context of ‘normal’ is conducted via several integrated but redundant mechanisms [Ackerman, 2004; Joyner, Charkoudian, & Wallin, 2008; Raven and Chapleau, 2014]. Maintenance of blood pressure is not constant and varies under different conditions both to avoid excessive and prolonged spikes, leading to potential organ damage, or excessive, prolonged reductions resulting in compromised oxygen delivery and organ dysfunction [Joyner et al. 2014; Raven and Chapleau, 2014]. BP regulation is adaptive with both acute and chronic mechanisms working and responding to physiological and pathophysiological triggers [Joyner et al. 2014; Raven and Chapleau, 2014]. Daily variations in arterial BP are contingent upon changes in several key regulatory mechanisms, including neural, local, hormonal and renal effectors [Ackermann, 2004; Raven and Chapleau, 2014]. Any deviation from "homeostatic normal" is monitored and re-established through changes in heart rate (HR), stroke volume (SV), and total peripheral resistance (TPR).

Changes in blood pressure are the result of variations in HR, SV and TPR within a relatively narrow range at rest [Ackermann, 2004; Joyner, Charkoudian and Wallin, 2008; Joyner et al. 2014]. Furthermore, many factors contribute to daily fluctuations in BP, including changes in body position, physical or emotional stress, and exercise [Ackermann et al. 2004; Eser et al. 2007; Franz et al. 1991; Joyner et al. 2014]. Moreover, daily fluctuations are necessary as BP requirements of a target organ or tissue are dynamic and based upon metabolic demands by that organ or tissue from a resting state [Ackermann, 2004; Chopra et al. 2011]. Generally, the physiological mechanisms responsible for changes in arterial BP during physiological challenges are adaptive and represented via multiple feedback control systems [Ackermann, 2004; Joyner et al. 2014; Raven and Chapleau, 2014]. A schematic of contributing physiological variables can be found in Figure 1.

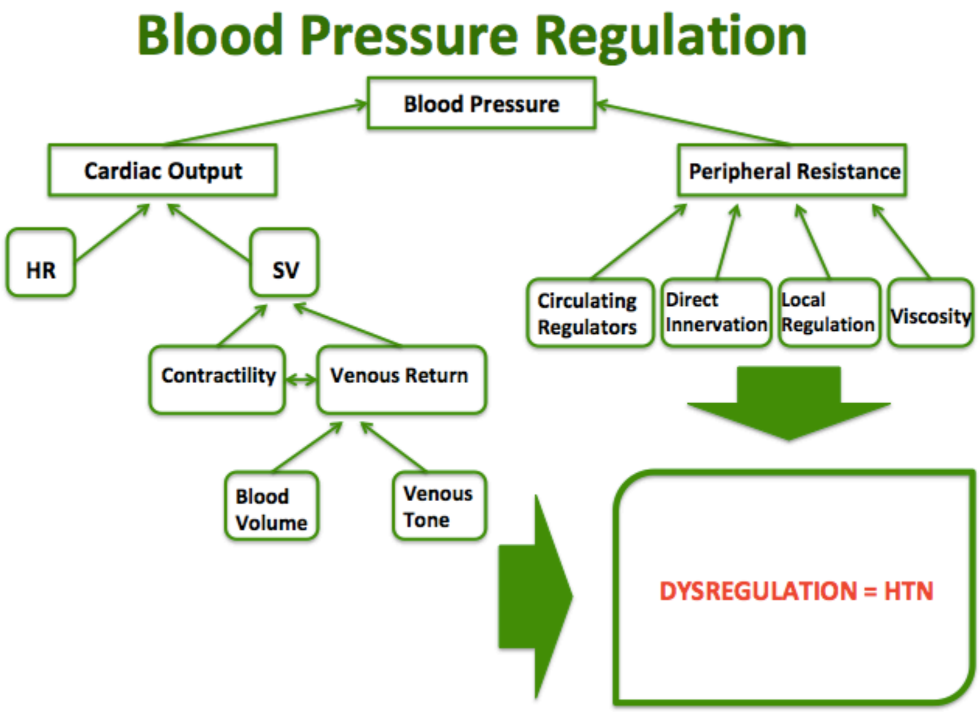


Figure 1. Schematic of physiological variables involved in BP regulation and ho homeostasis.

Cardiac Output (CO)

Two of the three major regulators of blood pressure are compounded to define cardiac output (CO); heart rate (HR) and stroke volume (SV) [Ackermann, 2004; Guyton et al. 1972; Joyner et al. 2014; Raven and Chapleau, 2014]. HR is the number of heartbeats per unit measure of time (e.g., 1-minute) whereas SV is the measured volume of blood ejected from the left ventricle with each contraction [Ackermann, 2004]. Thus cardiac output or 'Q' is the total flow of blood moved into systemic circulation over the course of a single minute, represented by the formula Q = HR x SV [Ackerman, 2004; Guyton, 2005]. At rest, both HR and SV are relatively stable, with each beat supplying adequate oxygen to the most metabolically active tissues, the heart and brain [Ackermann et al. 2004; Ichinose et al. 2014; Joyner et al. 2014; Raven and Chapleau, 2014; Rowell, 1993].

Total peripheral resistance (TPR)

Every tissue throughout the human body is subject to some level of resistance to flow [Ackerman, 2004]**.** Blood pressure is primarily influenced through two specific physiological variables, CO, as previously described and total peripheral resistance (TPR). A delicate balance between vasodilatory and vasoconstrictor responses at the periphery determine TPR [Ackerman, 2004; Joyner et al. 2014]. Moreover, TPR is dictated by luminal diameter and length of a vessel and blood flow is managed at the level of smaller arteries and feed vessels with the highest resistance to flow at the arterioles [Ackermann et al. 2004; Clifford et al. 2011; Levy et al. 2001]. Supplementary variables influencing TPR also include, the vessel network and physical properties of blood (i.e. viscosity and flow dynamics). Exercise is a primary modifier of blood flow and thus pressure, and is discussed below.

Resistance through a vessel (tube) is determined by physical forces (i.e., pressure and resistance) in accordance with Poiseuille's law [$\Delta P = 8\mu LQ/\pi r^4$]. Adaptive responses to exercise including resting vessel diameter and vascular density, are directly related to Poiseuille's law and are of considerable importance for long-term regulation of BP. A small increase in vessel diameter and resistance vessel cross-sectional area prompts a large change in TPR [Mayet and Hughes, 2003]. A level of evidence confirms that blood pressure is primarily regulated within the resistance vasculature, highlighting its importance in the regulation of systemic BP acutely and over time [Levy et al. 2001; Struijker et al. 1992; Vicaut et al. 1992].

TPR is also directly influenced by the sympathetic (excitatory) parasympathetic (inhibitory) nervous system and circulating neurohumoral molecules such as norepinephrine, epinephrine, and nitric oxide (NO) [Ackermann, 2004; Guyton, 1972; Joyner et al. 2014; Raven and Chapleau, 2014]. Vascular smooth muscle is influenced by competing vasoconstrictor (e.g. sympathetic activation and angiotensin II) and vasodilatory factors (e.g. byproducts of metabolism or brief ischemia and shear stress) [Ackermann, 2004].

Local regulation of arterial blood pressure and the microcirculation

Local control of blood pressure is the result of coordinated regulation of blood flow through larger conduit (delivery vessels) and smaller exchange vessels in the muscle (i.e. microcirculation). Regulators of local control include factors carried in blood or released from muscle and mechanical and myogenic stimuli and veno-arterial reflexes as previously described [Clifford, 2011; Gonzalez and Alonso, 2012; Laughlin et al. 1996]. Vasoactive compounds influence the state of vascular smooth muscle and can directly modify arterial BP [Guyton, 2000].

Endothelial cells produce vasoactive mediators that subsequently regulate flow and pressure [Ichinose et al. 2014]. Nitric oxide (NO) is a significant contributor to the vasodilatory response [Moncada, Palmer, and Higgs 1991]. Following bouts of exercise, metabolic end products of NO metabolism, including stable nitrates and nitrites have been measured in human blood plasma, indicating of exercise-induced hyperemia in skeletal muscle. Hyperemic responses enhance delivery of blood and nutrients to metabolically active tissue [Dyke et al. 1995; Gilligan et al. 1994; Miyauchi et al. 2003]. NO may not be the only active factor in exercise-induced hyperemia [Joyner and Wilkins, 2007]; adenosine tri-phosphate (ATP) adenosine diphosphate, prostaglandins and hydrogen ions may also be involved [Ichinose et al. 2014].

TPR is significant in the process of vascular conductance (flow) and pressure is regulated via the microcirculation [Levy, 2001; Struijker et al. 1992; Vicaut, 1992]. Pressure is gradually decreased from ejection pressure at the left ventricle to the capillary beds embedded deep within muscle [Pries, 1995]. Pre-capillary vessels in particular are exposed to the most substantial change in arterial pressure, approximately 70-90% of the drop in blood pressure is directed at these vessel beds deep in skeletal muscle [Delano et al. 1991]. Moreover, the microcirculation optimizes nutrient and oxygen delivery and prevents major disruptions within the existing vasculature in order to optimize capillary exchange [Levy, 2001]. Adaptations and improvements in exercise capacity are also found at the level of the resistance/exchange vessels, underscoring their importance.

Dysfunction within the resistance vasculature contributes to HBP and is the site where early HTN manifests [Levy, 2001; Pries, 2014]. Dysfunction may be occurring by several mechanisms including abnormal vasoconstrictor/vasodilator regulation, structural changes to the vasculature and reduced vessel density [Levy, 2001; Struijker, 1992]. Evidence suggests abnormalities in the microvascular network may be the result of existing HTN, or in fact may contribute to its development [Levy, 2001]. Therefore, the microcirculation is an evolving area of research; however, the most often prescribed antihypertensive medications have limited if any direct effects on the microcirculation in humans [Dahlof et al. 1993; Thybo et al. 1995]. Exercise, on the other hand, has been observed to increase vessel density, improve endothelial dependent vasodilation and upregulate the bioavailability of nitric oxide; note, all three variables are negatively affected by HBP, and are described below.

Local control of blood flow acts primarily at the endothelium. NO is a potent vasodilator that is produced during exercise; however, it may not act singularly to induce vasodilation. The microvasculature is important for BP regulation but also more recently has received attention for adaptations to exercise training and as a potential site of antihypertensive therapy [Levy, 2001; Pries et al. 2014].

Summary of arterial blood pressure control

BP is regulated via changes in heart rate (HR), stroke volume, and total peripheral resistance (TPR) within a relatively narrow range at rest [Ackermann, 2004; Joyner, Charkoudian & Wallin, 2008]. Various factors contribute to fluctuations in BP, such as changes in body position, physical or emotional stress, and exercise [Ackerman, 2004; Eser et al. 2007; Franz, 1991; Joyner et al. 2014]. Any change from "normal" is communicated to the periphery and changes in HR, SV and TPR are made to maintain homeostasis. In pathological conditions, the same occurs, but without appropriate control. The microcirculation is where the greatest change in pressure within the cardiovascular system occurs and where the early stages of HTN manifest. The microcirculation has also been given great consideration as a target for anti-HTN therapeutics; but current medications have produced underwhelming outcomes for direct effects on the microvasculature [Dahlof et al. 1993; Thybo et al. 1995]. There are believed to be several components related to inter-individual regulation of RBP. Genetic influences have received additional attention in recent years [Padmanabhan et al. 2010, 2015]. While not an element of this dissertation, the genetic influence of blood pressure control cannot be ignored if future clinicians, scientists, and exercise physiologists want to successfully manage the HTN epidemic with lifestyle strategies, including exercise.

Methods for Measuring Arterial Blood Pressure

Measurement of arterial blood pressure is a common clinical parameter providing snapshot of patient cardiovascular health. Most often BP is evaluated via several practiced techniques including non-invasive methods: auscultatory, oscillometric and invasive procedures including interarterial catheterization. Both clinical and home-based BP assessments are encouraged to identify daily variations in BP that can be used to approximate sustained elevations, deemed HBP or HTN [Whelton et al. 2017; Pickering et al. 2003]. Primarily, blood pressure has been assessed using non-invasive methods including sphygmomanometry and auscultation, automated oscillometry, and 24 hr. ambulatory BP [Ogedegbe and Pickering, 2010; Pickering et al. 2003]. In this dissertation, focus was placed on clinical based assessments as these have been done most often and routinely when diagnosing an individual with HBP [Pickering et al. 2003; Pickering 2005].

In this dissertation evaluations of RBP were conducted using an automated oscillometric device. Oscillometric BP measurements are based on the physiological variations in blood flow during the cardiac cycle (systole and diastole). The device is pre-programmed to inflate to supersystolic pressure and deflate to below diastolic pressure to indirectly estimate BP according to an empirically derived algorithm, specific to each device [Ogedegbe and Pickering, 2010]. Automated devices eliminate the element of inter-administrator bias, technical error and are less susceptible to ambient noise interference [Ogedegbe and Pickering, 2010; Pickering et al. 2003].

However, several limitations of automated oscillometry exist. These include lack of validated devices for in-home assessments and the device-specific algorithms also incorporate arterial stiffness as well as BP into outcome measurements [Pickering et al. 2003; Pickering et al, 2005]. This is significant as older adults (elderly, see chapter 2.) present with diminished arterial distensibility and increasing arterial stiffness. As a result, automated BP evaluations in these individuals may be grossly underestimated [Ogedegbe and Pickering, 2010; van Montfrans, 2001]. Furthermore, a lack of education on the appropriate guidelines for patients to abide by prior to a RBP measurement contributes to poor HBP evaluation and perhaps inappropriate diagnoses [Pickering et al. 2003;

Pickering 2005]. Despite several shortcomings, automated devices are being implemented at an increasing rate, are easy to use, and eliminate the likelihood for observer error between nurses and physicians in the clinic [Pickering et al. 2003]. Importantly, blood pressure does vary [~30% from a resting state, Millar-Craig et al. 1978], throughout the day from its lowest point upon waking, thus emphasizing the importance of tightly controlled measurement guidelines to establish an accurate RBP, described in Chapter 1. General Methods.

Current Issues with Measuring Blood Pressure

Measuring RBP is a standard clinical evaluation and is highly regarded for its simplicity [Whelton et al. 2017]. However, accurate measurements require considerable training and experience and are often misleading due to user error, faulty equipment, inherent variability in BP, and inconsistencies in methodology [Bailey and Bower, 1993; Chobanian et al. 2003; Pickering, 2005; Whelton et al. 2017]. Moreover, given recent changes to BP recommendations [Whelton et al. 2017], accuracy of measurements is ever more essential for appropriate categorization of patients along with evaluating cardiovascular disease risk and subsequent management of elevated BP [Whelton et al. 2017].

Standard procedures [Ogedegbe and Pickering, 2010; Pickering et al. 2003; Pickering et al. 2005] have been established and should be adhered to if clinicians hope to provide an accurate evaluation of their patients with appropriate diagnosis. These include appropriate cuff size, body position, arm position and dietary restrictions (caffeine and food) before blood pressure is taken. A more detailed description of the resting blood pressure guidelines adhered to in this dissertation is provided in the General Methods.

Pathophysiology of High Blood Pressure

HTN or HBP is known both in the community and to medical providers as the “silent-killer”, and it is also the number one modifiable risk factor for cardiovascular related morbidity and mortality worldwide. Moreover, in 90% of cases, the primary factor attributed to increased BP is idiopathic and of unknown origin, and is termed essential or primary HTN [Lilly, 2011]. In the remaining 10% and also far less common; secondary hypertension can be attributed to a definable cause [chronic kidney disease], and can be treated permanently or cured [Lilly et al. 2011]. Cures for essential HTN, however, are more elusive. The primary focus of this dissertation will be on the relationship between IET and essential HTN. To the knowledge of the author, limited if any data are currently available on the effects of IET when applied in the case of secondary HTN; this is an area that remains to be explored, as the disease implications are of considerable importance.

While speculative, an elevation in BP is believed to be the result of compensatory mechanisms associated with the derangement of long-term pressure control systems that contribute to homeostatic ‘normal’ [Joyner et al. 2014]. HBP is a non-homogenous disease. It is a complex mosaic of interactions among a genetic predisposition, the environment, as well as neural, mechanical and physiological perturbations at its foundation [Adamopoulos et al. 1975; Padmanabhan et al. 2015; Page, 1967].

To complicate matters further, HBP is primarily an asymptomatic condition, and only diagnosed when measured “high” following established guidelines [Chobanian 2003; Pickering et al. 2003,2005; Whelton 2017]. Current guidelines in Methods for Measuring and the General Methods indicate that two resting measurements on at least two different occasions are required prior to diagnosis [Chobanian, 2003; Pickering et al. 2003; Pickering et al. 2005; Whelton 2017;]. Clinicians and researchers must take into account the circadian variation of RBP along with acute effects or alterations in BP deemed the “white coat syndrome” [Chobanian, 2003; Ogedegbe and Pickering, 2010; Whelton 2017] prior to diagnosis.

Age and High Blood Pressure

While initially low in childhood, BP rises steadily during the first two decades of life [Hajjar et al. 2006]. According to both longitudinal and cross-sectional analyses, SBP increases each year in both men and women (0.29-0.91; 0.6-1.31 mmHg respectively) [Wolf-Maier et al. 2003]. Furthermore, DBP will rise, plateau, and potentially decline up to the fifth decade whereas SBP will continue to increase in most cases [Burt et al. 1995; Franklin et al. 1997; Goldstein 1994; Hajjar et al. 2001; Hajjar and Kotchen, 2003; Kannel, 1974] leading to a wide pulse pressure (PP). A wide PP is a contributing risk factor for cardiovascular morbidity and mortality [Aznaouridis et al. 2016; Benetos et al. 1998; Burt et al. 1995; Hajjar and Kotchen, 2003]. HBP is particularly of concern in adults >60 years due to risk factors like wide PP that can further exacerbate the incidence of heart attack, stroke, heart failure, and sudden death [Aznaouridis et al. 2016; Benetos et al. 1998]. Roughly, 60-75% of adults >75 years of age have HBP further contributing to the healthcare burden [Fu, 2012; Pimenta and Oparil, 2012]. Moreover, BP tends to vary widely in the population and there is a general increase in age secondary to arterial stiffening [Cooney & Pascuzi, 2009; Pescatello et al. 2004].

With age the endothelium becomes thicker and the walls atherosclerotic and calcified leading to diminished compliance and advanced arterial stiffening [Cooney & Pascuzzi, 2009; Fukutomi & Kario, 2010; Mayet and Hughes, 2003; Pinto, 2007]. HBP is in part the result of increased vascular resistance in both large vessels and small resistance arteries [Vlachopoulos et al. 2011]. To complicate matters further, age-related changes to arteries are very similar to those observed with HBP, making it more difficult to differentiate time course progression from disease associated arterial stiffening [Safar, 2005].

While sex differences was not a primary question investigated in this dissertation it is important to note that the prevalence of HTN is increased in men when compared to women, at least until the onset of menopause whereby this trend is reversed [Burt et al. 1995; Hart et al. 2009, 2011, 2012; Pescatello et al. 2004]. Menopause is a consequence of age, and in post-menopausal women the prevalence of diagnosed HBP exceeds that of age matched men after the 6^{th} decade of life [Burt et al.1995; Hart et al. 2011]. Such a trend is indicative of the importance for individualized and tailored management programs for both men and women at different life stages.

Current Recommendations for Management of High Blood Pressure

In the last several decades, target BP control has evolved. Primary outcomes for antihypertensive therapy include reducing the prominence of morbidity and mortality associated with cardiopulmonary and renal diseases and disorders [Chobanian et al. 2003; Whelton et al. 2017]. Until quite recently, BP goals in patients with HBP/HTN included achieving measurements of <140/90 mmHg [Chobanian et al. 2003]. However, a recent joint report published by the American College of Cardiology and the American Heart Association provides updates to previous guidelines by the Joint National Committee on Prevention, Detection Evaluation and Treatment of High Blood Pressure. HBP has been redefined and is now recognized as >130/80 mmHg, a change of -10 mmHg from previous guidelines for both SBP and DBP [Whelton et al. 2017].

This recommendation and others have come for the first time since 2003, and are intended for earlier intervention and prevention of HBP on a worldwide scale [Whelton et al. 2017]. Intervention strategies continue with a stronger emphasis on the importance of both home BP monitoring with validated devices and serial measurements prior to any diagnosis [Chobanian et al. 2003, Riebe et al. 2017 - ACSM Guidelines, 2017; Whelton et al. 2017]. In accordance with newly established guidelines individuals are now classified into one of four categories based on their RBP measures. Normal is classified as <120 and <80 mmHg; Elevated as 120-129 and <80 mmHg; Hypertension Stage 1 as 130-139 or 80-89 mmHg and Hypertension Stage 2 ≥ 140 or ≥ 90 mmHg [Whelton et al. 2017]. A significant change from past guidelines was the removal of pre-hypertension, replaced by Hypertension Stage 1. The rationale for this new categorization is based upon many observational, randomized controlled trial, lifestyle modification, and antihypertensive medication studies which have determined a significant association between SBP/DBP and increased risk for cardiovascular disease among others [Ettehad et al. 2016; Lewington et al. 2002; Whelton et al. 2017].

Because the development of HBP is complex, treatment strategies must also act through a variety of physiological pathways and or target organs/tissues to promote effective BP control. Presently, treatment avenues for HBP include lifestyle modification, diet, and exercise along with pharmacological interventions [Brook et al. 2013; Chobanian et al. 2003; Riebe et al. 2017 - ACSM Guidelines, 2017; Whelton et al. 2017,]. Special emphasis has been placed on alternative strategies for combatting the natural progression of increased BP in adults [Brook et al. 2013].

Lifestyle Modifications

Adopting a healthy lifestyle is recommended for initial management of HBP as well as its prevention [Appel et al. 2003a, b]. Strategies include weight reduction, reduced sodium consumption, following a DASH diet, and engaging in a regular aerobic, resistance, or a combination exercise program for approximately 150 minutes per week (30 minutes/day for ≥4 days per week). Aforementioned lifestyle modifications are encouraged and have shown to be especially effective with regards to BP lowering and maintenance [Brook et al. 2013; Elmer et al. 2006; Whelton et al. 2017; Williams et al. 2004]. Individual research studies support each strategy and positively influence BP (i.e. reductions) when incorporated singularly and in combination [Arburto et al. 2013; Blumenthal et al. 2000; Cornelissen and Smart 2013; Elmer et al. 2006; Reisin et al. 1978; Whelton et al. 1998; Williams et al. 2004.]. Prevention of HBP onset should also be addressed despite a past focus on existing HBP. A comprehensive meta-analysis has suggested that the onset of cardiovascular risk begins to appear with resting blood pressures as low as 115/75 mmHg [Lewington et al. 2002]. As such, early prevention strategies should be incorporated to mitigate the idiopathic rise in BP in currently normotensive individuals [Vasan et al. 2002]. Exercise, in particular, has received considerable attention, as a method for lowering HBP and is discussed below.

Pharmacotherapy

Resistant HBP or in individuals who do not adhere to lifestyle changes with regard to BP may be prescribed antihypertensive medications as a necessary next step for treatment [Whelton et al. 2002; Whelton et al. 2017]. Combination therapy (lifestyle modifications + medication) provides the most comprehensive avenue for HBP management [Whelton et al. 2017; Chobanian et al. 2003]. Clinical evidence indicates that the prescription of pharmacologics to treat HBP can lower the risk of heart attack, stroke, heart failure, and revascularization surgery in patients as well as prevent premature death [James et al. 2014; Jarari et al. 2016]. Antihypertensive medications to reduce HBP have been developed primarily with the intent to inhibit or enhance a single physiological mechanism. However, due to the complexity of BP regulation via several systems concomitantly, currently prescribed antihypertensive medications may have similar effector targets, however, may result in unpredictable and varied responsiveness in patients likely due to gene variants across patients [Padmanabhan et al. 2015].

Considering the broad mechanisms of action, it is recommended that pharmacological agents with documented effectiveness in the prevention of clinical events are used preferentially [Chobanian et al. 2003; Whelton et al. 2017]. Therefore, classes of anti-hypertensive medications meeting this 'standard' for recommendation include thiazide diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers (CCBs) [Chobanian et al. 2003; Mancia et al. 2007; Whelton et al. 2017].

However, despite the efficacy of prescribed pharmaceuticals to positively influence RBP for cardiovascular-related morbidity and mortality their effectiveness is also inconsistent [Hajjar and Kotchen, 2003]. This is further exacerbated by the fact that adherence to medication management or any other management strategy is low [Brook et al. 2013; Cooney & Pascuzzi, 2009; Pimenta and Oparil, 2012]. A National Institute of Health evaluation completed in 2014 identified that an estimated 50% of adults do not achieve recommended BP targets with medications alone [Hajjar and Kotchen, 2003; Yoon et al. 2015]. Primary barriers related to poor medication adherence may be a consequence of deleterious side effects and cost, both impacting poor BP control [Chobanian et al. 2003; Vawter et al. 2008; Whelton et al. 2017]. Medications alone are not enough to combat the growing problem of HBP; it is imperative lifestyle modifications be a first line intervention strategy then coupled with antihypertensive pharmacologics to achieve recommended targets in participants along the spectrum of normal to stage 2 hypertension [Millar et al. 2007; Whelton et al. 2017].

In summary, the management of HBP with combination therapy (lifestyle changes and medication) is not universally successful. Furthermore, poor adherence, medication side effects, cost, lack of health counseling and a general indifference towards lifestyle modifications contribute to a lack of effective control [Brook et al. 2013, Cooney & Pascuzzi, 2009; Pimenta and Oparil et al. 2012].

Exercise and High Blood Pressure

The association of physical activity and HBP has been evaluated at length [Brook et al. 2013; Cornelissen et al. 2011; Cornelissen and Fagard, 2005; Cornelissen and Smart. 2013; Fagard, 2011; Fagard and Cornelissen, 2007; Halbert et al., 1997; Kelley, 1997; Kelley and Kelley, 2001; Kelley and Kelley, 2000; Pescatello, 2004; Pescatello et al. 2015a]. Higher levels of physical activity and increased fitness are associated with a reduced incidence of HBP [Pescatello et al. 2004; Pescatello et al. 2015a]. Primarily the focus for exercise strategies include aerobic, resistance, and combination exercise programming and have been endorsed by the American College of Sports Medicine (ACSM) among other professional organizations with published guidelines and recommendations [Riebe et al. 2017 – ACSM Guidelines].

According to all major professional committees and organizations, aerobic exercise is the primary type of exercise encouraged for BP control [Pescatello et al. 2015a, b]. Aerobic activities include walking, cycling, and running for at least 30 minutes on most, if not every day of the week for a total of ~150/min of exercise/week [Brook et al. 2013; Pescatello et al. 2004; Pescatello et al. 2015a, b]. Aerobic activities lay emphasis on the cardiorespiratory responses to training. Research has shown the benefits of aerobic training are those acting primarily on skeletal muscle endurance and cardiorespiratory capacity by placing an appropriate stress on the cardiovascular system [Brook et al. 2013]. Continuous sessions of aerobic exercise are well documented, but developing evidence also reveals short interspersed periods throughout the day (e.g., 10-minutes) may also produce equivalent reductions in BP [Angadi et al. 2010; Bhammar et al. 2012; Ciolac et al. 2009; Jones et al. 2009].

Several encompassing Meta-analyses and systematic reviews of randomized control trials report a range of 1-9 mmHg reductions in BP [Pescatello et al. 2015a]. Of those reported the modality of exercise emphasized aerobic training. Presently, aerobic training is recommended as a first line exercise intervention based on the evidence supported by ~33 randomized control trials and Meta-analyses [Pescatello 2004; Pescatello et al. 2015a, b].

Dynamic resistance training or weight training involves a series of coordinated movements within a directed range of motion utilizing body weight or external resistance resulting in changes to the length and tension of the muscle [Cornelissen and Smart, 2013; Pescatello, 2004]. Historically, research has shown the positive effects of dynamic resistance training for increases skeletal muscle strength and endurance [Brook et al. 2013; Cornelissen and Fagard, 2005]. However, resistance exercise is known to elicit an exaggerated pressor reflex due to the mechanical and metabolic stimuli arising from contracting skeletal muscle [Kaufman & Hayes, 2002; Palatini et al. 1989]. Maximal resistance exercise can increase BP to a staggering 345/245 mmHg during maximal squat exercise [Palatini et al. 1989]. Periodic but significant increases in BP with resistance exercise is one primary apprehension by physicians for prescribing resistance exercise of any type for BP management [Brook et al. 2013; Williams et al. 2007; Thompson et al. 2007; Pescatello et al. 2004]. By contention exercise physiologists have argued that the rapid rise in BP observed during bouts of resistance exercise is responsible for the development of cardiac hypertrophy and increased vascular resistance, thus elevated BP as a result [Cornelissen and Fagard, 2005].

Compared to aerobic exercise training the evidence for BP lowering effects of resistance exercise training has been less persuasive [Cornelissen et al, 2011]. However, new evidence indicates this may not be the case, but perhaps the effect could be the initiation of a chronic hypotensive or BP lowering response, following several weeks of training [Pescatello, 2015a]. Meta-analytical evidence would now support and recommend incorporating resistance training exercise into a participant's overall fitness program [Cornelissen and Fagard, 2005].

Dynamic resistance exercise alone has been shown to promote modest reductions in RBP of 2 (DBP) to 3 (SBP) mmHg according to several publications [Cornelissen and Smart, 2013; Kelley and Kelley, 2000; MacDonald et al.2016]. While reductions were small, the significance of -2 mmHg in DBP at the population level could decrease the incidence of coronary heart disease and stroke [Cook et al. 1995; Whelton et al. 2002]. MacDonald [2016] reported that the greatest reduction in RBP came from those participants with higher RBP at baseline (~6 SBP / 5 DBP mmHg) compared to participants with normal RBP (~0 SBP / 1 DBP mmHg). Documented outcomes support the incorporation of dynamic resistance exercise training in adults with HBP and also suggest that reductions in RBP achieved may even exceed those evidenced in aerobic exercise programs [MacDonald et al. 2016]. The direct mechanism for lowered BP following bouts of resistance exercise remains to be fully identified due to conflicting and inconsistent results [Brook et al. 2013].

Concurrent with aerobic training ACSM now recommends 2-3 days of dynamic resistance training as a broad-reaching antihypertensive lifestyle therapy [Pescatello et al. 2004]. However, it is not well understood how combination programs influence HBP in adults [Corso et al. 2016]. Five Meta-analyses have explored the benefits of combination training and reductions in blood pressure range from 0-4 mmHg in clinical populations [Chudyk and Petrella, 2011; Cornelissen and Smart, 2013; Hayashino et al. 2012; Patyn et al.2013; Zou et al.2016]. A smaller reduction in RBP would suggest the outcomes of aerobic + resistance programs are less impressive than each exercise training mode alone. However, the health benefits from combination exercise programs exceed BP alone; affecting weight loss or maintenance, overall fitness, and muscular strength and endurance [ACSM Guidelines 2017].

Discussed in greater detail in Chapter 4, significant barriers to exercise training include time and cost associated with participation [Belza et al. 2004; Dishman, 1994a; Gillen and Gibala 2013; Lascar et al. 2014; Trost et al. 2002]. Thus, interspersed short bouts of low to moderate intensity exercise may be a preferred strategy to maintain adherence to exercise programming and have shown promise [Angadi et al. 2010; Bhammar et al. 2012; Ciolac et al. 2009; Jones et al. 2009; Pescatello et al. 2015a; Riebe et al. 2017 – ACSM Guidelines]. Nonetheless, both aerobic and resistance exercise training are not adhered to, thus limiting their efficacy for the control of BP long-term.

The Effects of Isometric Exercise Training

A “newly” established modality of exercise, shown to have an equally if not more profound impact on hemodynamic variables (e.g. RBP) when compared to aerobic and resistance exercise training programs [Cornelissen and Smart, 2013; Carlson et al. 2014; Cornelissen et al. 2011; Kelley and Kelley, 2010; Owen et al. 2010; Cornellissen and Smart, 2013] and anti-hypertensive medications [Millar, Swaine, McGowan, 2012]. Isometric contractions are a mode of resistance exercise whereby contracting skeletal muscle produces force but little gross change in length of the muscle occurs [Lind, 2011; Rowell, 1993]. A series of isometric contractions, repeated several times, several days per week is denoting of isometric exercise training (IET).

A seminal study observed a reduced incidence for HBP in adult males, in the workplace where job tasks incorporated bouts of isometric activity [Buck and Donner, 1985]. Since the study by Buck and Donner [1985] an expanding body of literature now exists exploring the use of low-moderate bouts of isometric exercise for improvements in RBP. IET is shown to be effective at lowering RBP in normotensive [Badrov et al. 2013a; Devereux et al. 2010; Gill et al. 2015; Howden et al. 2002; McGowan et al. 2007; Ray and Carassco, 2000; Wiles et al. 2010; Wiles et al. 2017], hypertensive [Badrov et al. 2013b; Baross et al. 2012], and medicated hypertensive [Badrov et al. 2013b] males and females within a broad age range utilizing several modalities of exercise [Lawrence et al. 2014; Millar et al. 2014]. Exercise modes include bilateral leg IET [Gill et al. 2015; Howden et al. 2002; Devereux et al. 2010] unilateral/ bilateral isometric handgrip [Millar et al. 2008; Badrov et al. 2013a, b; Badrov et al. 2016; Goessler et al. 2018; McGowan et al. 2006; McGowan et al. 2007a, b; Taylor et al. 2003; Wiley et al. 1992] and bilateral arm curl [Howden et al. 2002].

Within these studies, a wide range of exercise protocols comprised of differing intensities (10-50% of MVC; see chapter 1), durations (3-12 weeks), frequency (3-5 days per week) and total exercise volume [Lawrence et al. 2014; Millar et al. 2014] have been associated with significant reductions in SBP, DBP, and mean arterial BP (MAP). Furthermore, it is apparent that while significant reductions in hemodynamic variables are observed following IET (3-10 weeks), reductions are not permanent [Wiley et al. 1992]. According to the author, prior to the writing of this dissertation a paucity of data exploring the prolonged reductions in RBP (studies >10-weeks), additional support of IET in elderly adults & those with cardiac/pulmonary disease, the efficacy of home-based interventions, and the influence of systemic biomarkers for reductions in RBP following IET are lacking [Lawrence et al. 2014; Millar et al. 2014].

Isometric Exercise Training and Older Adults With High Blood Pressure

IET has also been reported to effectively lower RBP in non-medicated and medicated hypertensive adults [Badrov et al. 2013; Baross et al. 2012; McGowan et al. 2006; McGowan et al. 2007b; Millar et al. 2013; Peters et al. 2006; Taylor et al. 2003]. Peters and colleagues [2006] performed a 6-week (3 days/week) alternating unilateral isometric handgrip cohort study in non-medicated adults with hypertension (N=10; 52±5.0 years 146±11/ 90±7 mmHg). Both SBP (13 mmHg) and DBP (2 mmHg) were significantly reduced compared to baseline.

Conversely, Badrov et al. [2013b] completed a randomized control study in hypertensive adults medicated for HBP (51-74 yrs.). SBP (-8 mmHg), DBP (-5 mmHg), and PP (-4 mmHg) were significantly reduced in the exercise group (N=12) only after 10 weeks of alternating unilateral isometric handgrip exercise (30% MVC; 3 days/week). 83% of the individuals in the training group experienced a clinically relevant reduction in both SBP and DBP of ≥2 mmHg; importantly, only 83% of participants were being medicated for HBP [Badrov et al. 2013b]. These results imply that that not all those who participate in an IET program exhibit reductions in BP [see chapter 2-5 for detailed discussion]. In another study with medicated hypertensive (156±9 mmHg) subjects, SBP (-19 mmHg) and MAP (-11 mmHg) were significantly reduced after 10 weeks of alternating unilateral handgrip exercise [Taylor et al. 2003], however, no change in DBP was evident in this study. The results of these studies and others demonstrate the efficacy of IET at lowering RBP in older hypertensive individuals both medicated and non-medicated for HBP and highlight that effects of IET are not uniform.

Not only is lowering HBP in elderly individuals beneficial, but IET may be an appropriate engagement strategy in a population where over 50% of adults >65 years are not participating in any form of activity thereby exacerbating the risk of falls and frailty. Moreover, Stigglebout and colleagues [2006] identified that older adults are more likely to adhere to an exercise program that is not only organized, but where social interaction is involved [see chapter 2]. Self-efficacy measures and utilization of a social-psychological model of exercise adherence and participation are lacking as out outcome measures in various populations concerning exercise and especially IET. It is likely that these factors are involved in RBP adaptations to this type of training, however, limited if any data is available to support this notion and remains to be explored. Class-based interventions are a likely incentive for successful exercise engagement in this population leading to significant reductions in RBP. Therefore IET is a viable candidate in older adults to encourage maintenance of exercise with the potential outcome of lowering the number of daily medications taken, reducing adverse side effects and increasing quality of life.

Isometric Exercise Training and Cardiopulmonary/ Metabolic Diseases and Disorders

Adults and especially the elderly with HBP are often afflicted with multiple co-morbidities (e.g. cardiopulmonary disease, heart failure, stroke, type II diabetes and renal disease) and are taking a variety of antihypertensive agents simultaneously [Masoudi and Krumholz, 2003; Mukete and Ferdinand, 2015]. Due to the complexities of disease, a pathophysiological cross-talk contributes to poor BP control [Long and Dagogo-Jack, 2011]. However, exercise lowers BP and has a positive impact on other risk factors for cardiovascular disease including cholesterol and hyperglycemia control [Fagard, 2002; Fagard and Cornelissen, 2007].

Outpatient cardiac rehabilitation is an important component of the prevention and management of cardiovascular disease associated morbidity and mortality [Jolliffe et al. 2001; Taylor et al. 2004]. Aerobic exercise as previously described is the primary modality of exercise-based cardiac rehabilitation programs, but not all participants achieve HBP goals using this activity alone [Conraads et al. 2015; Jolliffe et al. 2001]. Resistance exercise may also promote reductions in BP after several weeks [Cornelissen and Fagard, 2005; Cornelissen and Smart, 2013; Kelley and Kelley, 2000; MacDonald et al. 2016]. However, clinicians especially, remain apprehensive to prescribe resistance exercise due to the potential for uncontrolled elevations in BP, in patients with compromised cardiovascular systems [Brook et al. 2013; Pescatello et al. 2004; Thompson et al. 2007; Vanhees et al. 2012; Williams et al. 2007].

Isometric exercise however is performed at low intensities and incorporates a small muscle mass, like handgrip [Lawrence et al. 2014; Millar et al. 2014]. Furthermore, contrary to traditional dynamic and static resistance exercise, IET at 30% of MVC has not been shown to elicit uncontrolled elevations in SBP or DBP during acute bouts isometric contractions in heart disease patients or the elderly, nor were modest elevations sustained for greater than 30-minutes post exercise [Araujo et al. 2011; Goessler et al. 2016; Olher et al. 2013]. Only 3 studies have been published investigating isometric exercise and patients with diagnosed cardiopulmonary disease, and these studies were limited to acute (1-2 bouts) exercise only [Araujo et al. 2011; Goessler et al. 2016; Olher et al. 2013], thus the training effects in this population are unknown. Active patients in cardiac rehabilitation programs could benefit from a training program adjunct to their existing rehabilitation. Data to support the efficacy of IET in patients currently undergoing combination therapy (diet, lifestyle, aerobic, and combination exercise) and that are currently diagnosed with significant cardiopulmonary disease is scant. HBP is common in this population and they could stand to benefit from IET, as HBP is independently the most powerful risk factor for exacerbating existing coronary heart disease [MacMahon et al. 1990; Escobar et al. 2002] stroke [MacMahon et al. 1990] heart failure [Kannel and Belanger, 1991] and renal disease [Klag et al. 1996]. Lowering HBP in individuals diagnosed with cardiopulmonary disease and multiple associated co-morbidities could result in improved disease management thus increasing quality of life in this population.

Isometric Exercise in the Lab vs. Home-Based Effectiveness

As described in the section High Blood Pressure Management, an important element in treating HBP relies on participant adherence and compliance with prescribed exercise [Pescatello et al. 2004]. Exercise is an important lifestyle modification to offset cardiovascular disease onset and progression [Pescatello et al. 2004]. Participant awareness of the benefits of exercise is an inadequate incentive to begin an exercise program [Aycock et al. 2015; Zimmermann et al. 2016]. As a result, a great number of individuals remain inactive for a variety of reasons. Zimmermann et al. [2016] reports that additional barriers to those already described previously are likely due to a combination of personal, social, and environmental factors, which may either encourage or inhibit participation.

To counteract inactivity a great deal of effort has been put forth in the promotion and marketing of exercise programs, however little research has been done on maintenance of exercise programs for periods exceeding 6-months [Stigglebout et al. 2006]. Furthermore, ~50% of individuals who start and exercise program will dropout within the first 6-months or they have no plan of starting to begin with [Carmody et al. 1980; Dishman, 1982; Dishman and Sallis, 1994; Oldridge et al. 1988]. This statistic is especially important as trends have indicated that there is a negative correlation between physical activity engagement and advanced age, with the highest percentage of inactivity in older adults >65 years of age. Moreover, exercise does require coordination and can be complex, contributing to poor adherence and desire to participate [Schutzer and Graves, 2004]. Finally, the word "exercise" itself perpetuates lack of participation, and has been viewed as a supplemental daily activity as opposed to a medical therapy [Schutzer and Graves, 2004]. Moreover, the 'side effects' of exercise may also be a deterrent (e.g. sweating and associated soreness) [Schutzer and Graves, 2004].

A recent emphasis has now moved toward home-based exercise programs to combat barriers and improve adherence [Anderson et al. 2017; Clark et al. 2010; Dalal et al. 2010; Fakhry et al. 2011; King et al.1991]. However, available data on the effects of home-based programs is limited and has incorporated traditional exercise programming only (aerobic and dynamic resistance) [Cornelissen, 2009; Farinatti et al. 2005; Farinatti et al. 2016; Hua et al. 2009; Johnson et al. 2014; Staffileno et al. 2007]. Comparably, IET requires low-moderate intensity and 80% less time to achieve equivalent if not greater reductions in RBP [Carlson et al. 2014; Cornelissen and Smart, 2013]. Moreover, the equipment and level of physical ability required is minimal [Millar et al. 2008; Mostoufi-Moab et al. 1998].

With the expanding volume of IET literature in a recent 10-year period, the majority of IET studies published incorporate laboratory-based techniques. In the laboratory, testing conditions are controlled and the results support claims that IET can achieve substantial reductions in RBP in a short period with as little as 30-minutes of exercise per day, several days per week [see section The Effects of Isometric Exercise Training]. Furthermore, a limitation of laboratory testing is that investigations while controlled are limited and often incorporate expensive equipment and require a substantial time commitment of participants along with travel to and from the testing facility [Belza et al. 2004, Lascar et al. 2014, Trost et al. 2002; Gillen and Gibala 2013]. Such barriers and others discussed above, contribute to the current limitation of IET to be used more broadly for community-based investigations.

Detailed in preceding sections, IET has been conducted utilizing IHG, bilateral leg extension, and bilateral arm curl and the majority of studies have been prescribed and supervised in the laboratory for 3-10 weeks. Home-based IET would provide a valuable alternative to traditional exercise for training given it not only significantly lowers BP, but it can be performed simply, safely, and out of convenience anywhere [Ray and Carassco, 2000; Wiles et al. 2017]. Several investigators have attempted to implement home-based exercise with IHG, however, these studies in part were completed 2 days per week in the laboratory and 1-3 days in the home [Millar et al. 2008; Badrov et al. 2013; Millar et al. 2013]. Regular engagement with researchers likely contributes to exercise adherence and successful reductions in RBP in these studies.

In the last year, two IET studies have been published whereby exercise was completed entirely in the home. Each respective study incorporated a different modality and study design further contributing to the inconsistencies of IET programs. Wiles et al. [2017] was the first investigator to publish an IET study entirely in the home, utilizing a novel wall squat protocol. The second study was a head to head comparison of IHG exercise with self-selected aerobic endurance exercise for 8-weeks paired with telecoaching for participant monitoring. Both studies achieved significant reductions in RBP [Goessler et al. 2018]. Despite a general success, the direct comparison of traditional laboratory based IET vs. home-based video-based IET has not been investigated.

Potential Mechanisms for IET-induced Reductions in Resting Blood Pressure

Described in detail previously blood pressure is determined by the coordinated regulation of changes in HR and SV (CO) and TPR. Therefore it is probable that adaptations that arise from participating in IET are acting through one or all three of these variables [Wiley et al. 1992; Lawrence et al. 2014; Millar et al. 2014]. Despite the success of IET in reducing RBP, mechanisms for BP reduction are not well understood and current attempts to describe the potential mechanisms have produced inconsistent results [Lawrence et al. 2014; McGowan et al. 2006; McGowan et al. 2007a,b; Millar et al. 2014].

Proposed by Lawrence et al. [2014] it is highly likely that the mechanisms for IET are phasic and multifactorial based upon existing knowledge of time-course exercise training adaptations. Duration of IET programs has been discussed with regard to both early and longer-term training adaptations [Lawrence et al. 2014; Millar et al. 2014]. Shorter duration IET programs of 3-4 weeks have elicited significant reductions in BP [Badrov et al. 2013a; Gill et al. 2015; Wiley et al. 1992]. Stimulation of skeletal muscle afferents (specifically, III, mechanoreceptors; and IV metaboreceptors) or at the level of autonomic nervous system (heart rate variability; baroreceptor modulation) may act through immediate and short-lived effects [Choi et al. 2013; Fisher and White, 2004; Fisher et al. 2013; Millar et al. 2013; Secher, 2011; Secher and Amann, 2012; Rondon et al. 2006; Ray and Carassco, 2000; Taylor et al. 2003; Wiles et al. 2010]. Studies have found that, muscle sympathetic nerve activity (MSNA) translated via muscle III and IV afferents are over stimulated in hypertensive individuals [Choi et al. 2013; Rondon et al. al. 2006]. Regular exercise has been shown to lower activation of MSNA, particularly in response to transient exposure to metabolic byproducts of anaerobic metabolism (i.e. lactate) [Fisher and White, 2004]. Relevant to this work, reductions in MSNA have been observed following IET [Devereux et al. 2012]. However, results are inconsistent between investigations, as other researchers found no effects of IET with respect to improvements in MSNA [Ray and Carrasco, 2000] further contributing to the inconsistencies for skeletal muscle afferent modulation and BP control.

Only a few studies explored the direct relationship of both CO and TPR following 4 [Devereux et al. 2010; Devereux et al. 2015] and 8 weeks [Wiles et al. 2010] of IET. Significant reductions in RBP occurred in all three investigations, however, only one study observed an improvement in hear rate recovery following 4-weeks of bilateral leg IET [Devereux et al. 2015]. Moreover, no significant changes in CO or TPR were observed limiting the capacity for a thorough evaluation of CO and TPR as involved processes in adaptations to IET.

Millar [2007] explained that 3-4, and up to 8-weeks of training may not appropriately represent a fully hypotensive effect. Longer periods of training a may be influential on BP regulatory variables, like total peripheral resistance (TPR) [Fagard and Cornelissen, 2007] in turn requiring a longer stimulus period to allow for adaptations to occur. Described previously, BP is primarily regulated at the level of the resistance vasculature, wherein modifications may be measured by changes in TPR [Haddy, 1968; Levy, 2001; Millar et al. 2014; see regulation of arterial blood pressure previously]. During an isometric contraction changes of vascular shear stress may initiate changes in endothelial function and subsequently TPR. Shear stress is the flow of blood across the surface of the endothelium and it modulates endothelial derived vasoactive molecules, angiogenesis and inflammation [Kolluru et al. 2010]. Short periods of enhanced shear stress during isometric contractions may also enhance bioavailability of NO, endothelial dependent vasodilation, and vasoactivity in the resistance vessels leading to reductions in RBP [McGowan et al. 2006; Badrov et al. 2013a, b; Badrov et al. 2016].

With IHG, improvements in local reactive hyperemia shortly after contraction have been evaluated in participants following 4 or 8 weeks of training [McGowan et al.

2007; Badrov et al. 2013]. McGowan [2007a] found localized improvements in nitric oxide-dependent vasodilation in the exercising arm of hypertensive adults following 8-weeks of IHG. It is likely these outcomes are due to enhanced shear stress during and after isometric contractions. Therefore, improvements in TPR via enhanced bioavailability of NO and endothelial dependent vasodilation would be significant in hypertensive adults, as endothelial dysfunction is common in this population [McGowan et al. 2007a; Schiffrin et al. 2004]. However, conflicting evidence by McGowan et al. [2007a, b] may suggest IET is not uniformly effective at eliciting improvements in endothelial function in adults with normal blood pressure [McGowan et al. 2007b] versus high blood pressure [McGowan et al. 2007a]. The author proposes the potential of an alternative mechanism however this has not yet been identified. Green et al. [2004] suggested health status (high blood pressure) is likely an important variable concerning endothelial responsiveness and basal production of NO in response to exercise.

Despite conflicting results. Some observations may be representative of long-term functional and structural changes within the resistance vasculature concomitant with local conduit artery dilation, thus playing a role in exercise induced BP reductions [Edwards et al. 2007; Levy, 2001; McGowan et al. 2007a; Millar et al. 2014]. Described previously, the microcirculation and resistance vessels are primarily responsible for modulating arterial BP [Badrov et al. 2013; Levy, 2001, Pries, 2014]. Therefore, improvements within the resistance vasculature are especially important in persons with elevated BP.

Badrov et al. [2013] were the first to explore such adaptations utilizing 3x/week and 5/week of IHG at 30% MVC for 8 weeks with a randomized controlled design. Not only was blood pressure reduced in both IHG (IHG3/week = -6mmHg; IHG5/week = -6 mmHg) training groups, but reactive forearm hyperemia measured by strain-gauge plethysmography (an induce of resistance vessel function) was also significantly enhanced (IHG3 = +10mL/min/100mL; IHG5 = +12mL/min/100mL).

The authors further proposed that improvements in their study may have also been due to shear stress in the exercising forearm [Badrov et al. 2013]; therefore mediating endothelial-derived NO production also noted previously by McGowan and colleagues [2006, 2007a&b]. Shear stress may also act on peripheral vasculature by enhancing the surface area of the microcirculation. Kolluru et al. [2010] observed that endothelial cell remodeling occurs after only 15-minutes of shear stress, despite the inhibition of NO. Further supporting evidence of enhanced blood flow, conductance, and resting conduit vessel diameter have also been presented as evidence of vascular remodeling and lowered RBP following bouts of IET [Baross et al. 2012]. The author of this dissertation proposes that the up-regulation of locally produced but systemically vasoactive mitogens and cytokines could play a role in the hypotensive response over several weeks of IET exposure, but studies investigating vascular growth factors and inflammation have not yet been conducted.

In summary, it is highly likely multifactorial mechanisms are involved in adaptations to IET [Hess and Smart, 2017; Lawrence et al. 2014; Millar et al. 2014]. Skeletal muscle afferent stimulation [Choi et al. 2013; Ray and Carassco, 2000; Rondon et al. 2006], and affects of the ANS [Millar et al. 2013; Taylor et al. 2003; Wiles et al. 2010] may be responsible for lowering BP in the short term; while improvements in oxidative stress [Peters et al. 2006], endothelial dependent flow-mediated dilation, enhanced bioavailability of NO; and transient changes in TPR may result with extended training [Badrov et al. 2013, 2016; Baross et al. 2012; McGowan et al. 2006; McGowan et al. 2007a, b; Peters et al., 2006]. Results of prior investigations are equivocal having assessed their respective variables in singular fashion. Moreover, it is apparent that adaptations are likely contingent upon RBP at the onset of training [Millar et al. 2007]. While reductions in RBP have been observed in all BP categories, discrepancies in mechanistic responsibility between hypertensive and normotensive adults are likely and require additional investigation [Green et al. 2004; McGowan et al. 2006, 2007 a, b;].

Supportive Evidence For Systemic Biomarkers As a Mechanism of IET

New intervention strategies whereby short bouts of reduced blood flow as a result of an applied tourniquet or cuff, cuff application + low intensity resistance exercise or sustained muscle contraction may promote an up-regulation in the activity of vasoactive pathways as well influence inflammation systemically. Modalities include blood flow restriction (BFR) training remote ischemic conditioning (RIC) and physiological ischemic training (PIT) [Hess et al. 2015; Larkin et al. 2012; Ni et al. 2017; Shimizu et al. 2016; Shimizu et al. 2009; Takarada et al. 2000]. Many investigations in humans have explored these intervention strategies and subsequent responses following vascular occlusion or ischemia training. The proceeding sections will describe these interventions as well as the potential relationship IET may share, thus providing evidence for the effects of systemic biomarkers leading to reductions in RBP.

Blood Flow Restriction Exercise and Interventions

The muscle strength effects of restricting blood flow concomitant with low to moderate resistance exercise training, termed BFR exercise have been studied extensively in humans [Cezar et al. 2016, Larkin et al. 2012; Loenneke et al. 2011; Shimizu et al. 2016, Takarada et al. 2000;]. BFR involves the application of a tourniquet or pneumatic cuff to the proximal end of an exercising limb during a resistance exercise session, repeated multiple times [Cezar et al. 2016; Larkin et al. 2012; Shimizu et al. 2016, Takano et al. 2005; Takarada et al. 2000]. Benefits of BFR include improvements in muscle strength and hypertrophy [Loenneke 2011, Moore et al. 2004, Takarada 2000], along with enhanced production and circulation of several vasoactive and inflammatory biomarkers [Green et al. 2004; Hess et al. 2016; Shimizu et al. 2016]. Importantly, BFR induces a state muscular ischemia, whereby excessive production and secretion of vascular endothelial growth factor (VEGF), growth hormone and interleukin-6 (IL-6) have been reported [Patterson et al. 2013, Takano et al. 2005, Takarada et al. 2000]. It is likely that proposed strength gains with BFR are achieved through hypersecretion of these substances.

Notably, in addition to improvements in strength, circulating VEGF is known to influence the vascular endothelium [Fujita et al. 2007], vessel growth [Ji et al. 2007], and peripheral vascular resistance [Napoli et al. 2003, Tivesten et al. 2004] respectively. Production of vasoactive factors by BFR or related exercise supposedly improves endothelial function by shear stress enhanced endothelial nitric oxide synthase (eNOS) expression as previously described, particularly in skeletal muscle [Green et al. 2004]. Shear stress is the result of the change in movement of blood flow across the endothelial surface [Bloor et al. 2005; Kolluru et al. 2010] and is enhanced during blood flow obstruction [McGowan et al. 2006] like IET. These changes in normal blood flow likely contribute to changes in vascular regulation [McGowan et al. 2006; Badrov et al. 2013] and resistance vessel structure and function [Badrov et al. 2013; Baross et al. 2012]. Physiological effects of circulating substances like VEGF and IL-6 may determine the potential for sustained improvements in RBP following a period of training.

Effects of Remote Ischemic Conditioning

Remote ischemic conditioning was originally developed for myocardial protection [Murry et al. 1986] prior to undergoing open heart surgery. RIC is phenomenon whereby, intended restriction of blood flow followed by subsequent reperfusion of tissue stimulates signaling pathways via secreted diffusible factors, lowering blood pressure and promoting systemic organ (brain, liver, heart, and skeletal muscle) protection [Epps et al. 2016; Hausenloy and Lim, 2012; Hausenloy and Yellon, 2008; Loukogeorgakis et al. 2005, Madias, 2011, 2014, 2015]. Mechanisms underlying RIC occur by three distinct events 1) initial effects at the remote tissue (i.e., brief ischemia) stimulates production and release of endogenous protective factors 2) downstream tissue targeting in response to upstream signaling, likely from systemic blood factors or activation of systemic responses and 3) direct effects at the target tissue [Hausenloy and Yellon, 2008; Tapuria et al. 2008]. RIC protocols utilize super systolic, ~ >200 mmHg external blood flow occlusion while the subject is at rest (i.e., no muscle contraction) [Hausenloy and Lim, 2012]. A subject is fitted with a standard blood pressure cuff, which is rapidly inflated at a given percentage of SBP and blood flow is occluded for periods of 3-5 minutes

[Hausenloy and Lim, 2012]. Occlusion and reperfusion of blood flow is performed over several repetitions, several times per week; an intervention design that aligns similarly with IET.

RIC may represent a systemic stimulus for blood vessel responsiveness [Jones et al. 2014] similar to that of traditional exercise training. A single session of RIC may have positive effects on endothelial function as well as immune and anti-inflammatory responses [Jones et al. 2014; Kharbanda et al. 2001; Kimura et al. 2007; Kostantinov et al. 2004] another contributor to BP regulation. While results are conflicting, acute effects indicate a potential for long term, sustained changes in blood vessel structure and function [Jones et al. 2014] and is supported by the observation where RIC induces elevations in VEGF similarly with BFR training described previously [Kimura et al. 2007; Ueno et al. 2016], which has the potential to improve the microcirculation via angiogenesis [Jones et al. 2014]. While not the primary focus of RIC, reductions in RBP have also been observed [Jones et al. 2014; Madias et al. 2011,2014, 2015; Maior et al. 2015]. Both BFR and RIC partially or entirely reduce blood flow thereby initiating intrinsic physiological adaptations in conduit vessels/ microcirculation and skeletal muscle. However, these interventions achieve their effects through different means; BFR via cuff occlusion with low load muscular contractions and RIC with a pneumatic cuff inflated to a supersystolic pressure during rest.

An alternative strategy, physiological ischemic training (PIT) may provide an avenue of research connecting these two methodologies (restriction of blood flow by muscle contraction + muscle-derived or systemic blood factors) to promote the greatest response at endothelium and across the microvascular landscape.

Physiological Ischemia Training and Isometric Contractions

Similar to the effect of BFR and RIC, physiological ischemic training (PIT) restricts normal muscle blood flow [Ni et al. 2015; Hess and Smart, 2017]. For blood flow restricted exercise interventions the notion of systemic effects on blood vessel function is supported by recent data on RIC. What differentiates PIT from RIC and BFR is that PIT incorporates exercising muscle mass with intense contraction (e.g. isometric) induces localized ischemia [Ni et al. 2015, 2017] as opposed to a BP cuff or tourniquet.

Ischemia or inadequate blood perfusion, in turn, leads to tissue hypoxia. Hypoxia is a potent stimulator of HIF-1a activation in skeletal muscle and is a well-recognized transcription factor for activating downstream targets of tissue adaptations to hypoxia (e.g., VEGF) at the endothelium [Ohno et al. 2012]. VEGF is a primary regulator of blood vessel growth and is enhanced during restricted exercise [Patterson et al. 2006, Shimizu et al. 2016, Shweiki et al. 1992; Takano et al. 2005]. As a result, production and distribution of VEGF would stimulate vascular growth, increasing the surface area of resistance vessels embedded deep within skeletal muscle. Adaptations would inherently have direct effects on TPR and has been described previously as an important element in BP regulation [Hess and Smart, 2017; Levy et al. 2001; Thijs et al. 2013; Tinken et al. 2010]. However, the effects of metabolites (e.g. HIF-1α and subsequently VEGF) following isometric contraction induced ischemia has only been postulated [Stiller-Moldovan et al. 2012; Wang et al. 2014] and only one study has investigated its potential with outcome effects observed in the intact myocardium of patients with coronary artery disease [Lin et al 2014].

HBP is associated with chronic low-grade inflammation, characterized by two-threefold increases in systemic cytokines like tumor necrosis factor alpha (TNF-α) and IL-6 [Petersen and Pedersen, 2005]. Higher systemic levels of TNF-α alone are correlated with increased BP [Edwards et al. 2007], accompanied by increased adiposity (whole body fat mass) and a sedentary lifestyle [Petersen and Pedersen, 2005; Ramseyer et al. 2013]. Resistance exercise, in particular, is postulated to suppress the inflammatory cascade and could be implicated for anti-inflammatory benefits [Mathur and Pedersen, 2008]. A single bout of resistance exercise will increase plasma cytokine levels initially. However, lower basal cytokine levels have been reported following repeated bouts over several weeks [Calle and Fernandez, 2010]. According to present data, no consensus on the effects of resistance exercise to have anti-inflammatory effects has been reached.

Interleukin-6 is a cytokine, determined to have both inflammatory and anti-inflammatory effects and is the subject of an ongoing debate, however, it appears to be linked to its derived location (anti-inflammatory from muscle; inflammatory from adipose tissue) [Febbraio and Pedersen, 2002; Pedersen, 2009; Pedersen and Febbraio, 2008; Tilg et al. 1997]. Several detailed reviews have identified that muscle-derived IL-6 has an anti-inflammatory role in response to exercise and has been rebranded a 'myokine' or muscle-derived cytokine [Brandt and Pedersen, 2010; Mathur and Pedersen, 2008; Pedersen and Febbraio, 2008; Petersen and Pedersen, 2005]. Furthermore, muscle-derived IL-6 is purported to reduce inflammation by stimulating the release of other anti-inflammatory cytokines like IL-1a and IL-10 [Steensberg et al. 2003], which have also been observed following bouts of resistance exercise [Hirose et al. 2004; Izquierdo et al. 2009]. A secondary effect of IL-6 is the inhibition of TNF-a, a well-known inflammatory cytokine previously described [Petersen and Pedersen, 2005]. Exercise-induced, anti-inflammatory benefits through the interaction of contracting skeletal muscle tissue and circulating cytokines is an evolving area of research [Petersen and Pedersen, 2005] and has not been evaluated following IET.

Chronic low-grade inflammation, dysfunction of microcirculation, reduced vessel density and negative affects on TPR may be important elements leading to HTN [Levy et al. 2001; Edwards et al. 2007]. Thus, IET may be an appropriate physiological stressor to induce structural changes via secreted elements at the vasculature, thereby improving vessel density and TPR and reducing biomarkers of systemic inflammation [Hess and Smart, 2017].

The effects of PIT have been observed in rabbits over the course of 4-weeks applied 8x daily and were shown to up-regulate VEGF, facilitating angiogenesis systemically [Shen et al. 2009; Zhao et al. 2011]. Moreover, a single study has been completed in human heart disease patients using isometric handgrip exercise. Results of that study align with RIC whereby myocardial collateral vascularization was significantly improved in patients who completed IHG compared to controls [Lin et al. 2014].

The author of this dissertation acknowledges this was a single study, however, additional data identifying the changes in systemic biomarkers following brief bouts of ischemia (RIC, BFR and PIT) which are similar to that of an isometric contraction are nonetheless compelling to suggest a potential mechanism involved in a remote signaling cascade. The author hypothesizes that isometric contractions establish an environment conducive to the production and circulation of factors like IL-6 and VEGF. Past investigations have shown significantly elevated VEGF, IL-6, and decreased TNF-α following BFR or ischemia training, but RBP was not evaluated in these studies. Therefore a direct relationship has not yet been identified.

Reactive hyperemia is a vasodilatory response that occurs following brief bouts of blood flow obstruction [Hayoz et al. 1995; Philpott and Anderson, 2007]. Reactive hyperemia and enhanced endothelial dependent vasodilation have been observed with IET [Badrov et al. 2013 a,b; Mcgowan et al. 2007]. Additional research has shown that total occlusion of intramuscular blood flow during an isometric contraction occurs at 55-75% MVC [Rowell, 1993]. However, partial blood flow obstruction during handgrip exercise playing into the role of shear stress has been suggested at MVC intensities as low as 10-14% [Baross et al. 2012; Hess et al. 2016; Wiles et al. 2010]. Reductions in RBP have been achieved using a range of MVCs [Lawrence et al. 2014; Millar et al. 2014]. Thus, 10-30% MVC would be an appropriate intensity wherein effects on BP may be observed as a result of several weeks of exposure to pre-post reactive hyperemia.

Summarizing Restricted Exercise and Local Ischemia: A Significant Stress That Leads to the Activation of Cellular Homeostatic Pathways in the Circulation

RIC, PIT and BFR, when applied clinically or as a part of an exercise intervention, significant health benefits have been observed. Effects include systemic organ protection [Hausenloy and Lim, 2012; Hausenloy and Yellon et al. 2008], hypotensive effects [Madias 2011, 2014, 2015; Maior et al. 2015; Neto et al. 2015], and improvements in endothelial dysfunction [Heusch et al. 2015] and muscle strength [Loenneke 2011; Moore et al. 2004; Takarada 2000]. Concerning IET, periodic reduced blood flow (ischemia) and tissue reperfusion (reactive hyperemia), repeated several days per week for several weeks is likely to initiate adaptive ischemia responses, in turn influencing HBP [Hess and Smart, 2017].

The Influence of Muscle Mass on Exercise Outcomes

A degree of adaptation to exercise is positively correlated with muscle mass exercised [Galvez et at 2000;, Howden et al. 2002; Mitchell et al. 1980; Seals et al. 1983; Seals 1989; Williams 1991]. Cardiovascular (CV) responses (SBP, DBP, mean arterial pressure) to isometric contractions are well known. A direct relationship exists between muscle mass (isometric handgrip, isometric bilateral leg extension) and increases in cardiovascular responses (HR, mean arterial pressure) at the same relative exercise intensity, 30% MVC [Seals et al. 1983]. Evidence suggests that CV responses correlate with IET induced reductions in RBP with training. Researchers have attempted to predict the significance of IET induced reductions in RBP based upon stress reactivity testing [Badrov et al. 2013; Millar et al. 2009].

These data further indicate a likelihood that muscle mass is an important variable related to BP reductions following IET. Published papers and review articles have debated whether contracting muscle mass may be an important factor related to blood pressure reductions with IET [Howden et al. 2002; Iellamo et al. 1999; Lawrence et al. 2014; Millar et al. 2014]. Howden and colleagues [2002] completed a study comparing upper extremity versus lower extremity IET. RBP reductions were observed within groups, but no difference between groups was observed, although exercise intensity was lower in the larger muscle mass (legs) group [Howden et al. 2002]. Moreover, in a review of potential mechanisms for IET induced RBP reduction, Millar and colleagues [2014] suggest that RBP responses to IET are muscle mass independent where Lawrence et al. [2014] propose otherwise. Thus, questions regarding the importance of muscle mass are unresolved.

Summary of Background and Significance

The results of previous investigations highlight the need for new and expanding avenues of research on age, presence of cardiopulmonary disease, home-based effectiveness, and mechanisms related to differences in BP adaptations to IET. If individual responsiveness and maintenance effects of IET are dependent upon age, cardiopulmonary disease, length of training, systemic biomarkers, or muscle mass, individualized exercise prescriptions in accordance with guidelines from the American College of Sports Medicine would be required to effectively lower RBP. Despite the apparent connection between IET associated control of arterial RBP, limited research has attempted to identify the most important protocol elements contributing to changes in BP. Therefore, impeding the ability of investigators to develop and refine IET protocols for maximum responsiveness and HBP control.

Specific Aims

Given the established but discrepant reductions in RBP following IET in subjects with normal, pre-HBP, and diagnosed HBP, I propose the following aims:

Specific Aim 1: <u>To determine the efficacy of long duration IET (12-weeks) to promote reductions in RBP in older but recreationally active adults and to determine maintenance effects of RBP following an extended detraining period.</u> This was accomplished by incorporating an established isometric handgrip training protocol comprising 4, 2-minute handgrip contractions at 30% of maximal voluntary contraction, 3 days per week for a total of 12-weeks. The novelty of this investigation includes a monitored detraining period of 6 and 12-weeks after the completion of IHG.

The objectives for this aim are to:

1. Compare RBP measures among groups to determine group differences.

2. Compare RBP measures among groups during and following an extended period of detraining and determine if duration of training is related to prolonged reductions in RBP.

I hypothesized that 12-weeks of isometric handgrip (IHG) training would produce significant reductions in resting blood pressure (RBP) when performed by aged adults (>60 years) from a local senior center. Additionally, I hypothesized that resting blood pressure measures will be significantly lower than pre-training measures six weeks after training has concluded (i.e. detraining)

Specific Aim 2: To explore the efficacy of IET to promote reductions in RBP in patients with diagnosed cardiopulmonary diseases and disorders. This was accomplished by incorporating the same IHG protocol as described in specific aim 1, but integrated into a pre-existing outpatient cardiac rehabilitation program affiliated with the Sanger Heart and Vascular Institute in Concord, NC.

The objectives for this aim are to:

1. Compare RBP measures among groups to determine group differences.

2. Examine if there is a relationship between disease severity and current antihypertensive medications and responsiveness to IHG exercise.

I hypothesized that 12- weeks of IHG training will produce significant reductions in RBP when performed by members of an outpatient cardiovascular and pulmonary rehabilitation program. Additionally, I hypothesized that resting blood pressure measures will be significantly lower that pre-training measures six weeks after training has concluded (i.e. detraining).

Specific Aim 3: To investigate whether a 12-week home-based IET program could mirror significant reductions in RBP currently established in the IET literature and to provide additional support for prolonged detraining adaptations to IET for BP management in line with Aim 1 and 2. Aims were accomplished by development and implementation of a home-based IHG training protocol aimed at reducing RBP in hypertensive adults. Furthermore, a three-group design was used with a direct comparator group of traditional face-to-face (laboratory-based) IET to address efficacy of home-based designs with that of documented laboratory-based protocols.

The objectives for this aim are to:

1. Develop a home-based IHG exercise training video with exercise program to be implemented outside a laboratory environment for home or office use.
2. Perform a direct comparison of RBP measures between face-to-face and home-based IHG exercise with a control to determine group differences.
3. To further explore in line with Aim 1 and 2, the potential for sustained RBP adaptations to home-based IHG during a monitored detraining period (6-weeks).

I hypothesized that home-based IET program participants will experience equal reductions in RBP when compared to face-to-face IET and delayed treatment/ control groups. Additionally I hypothesized that completion of 12-weeks of isometric handgrip training will produce significant reductions in blood pressure that are measured below baseline for an additional 6-weeks (detraining) across exercise groups (home-based IET and face-to-face based IET). Finally, I hypothesized that adherence in home-based programming will be equal or better compared to the laboratory-based training group

Specific Aim 4: To examine the effects of a both an acute bout of repeated isometric contractions (x6) and responses to a training program (6-weeks) on the release of selected peripherally circulating vasoactive and inflammatory biomarkers relative to muscle mass exercised. This was accomplished by, comparing RBP and circulating vasoactive and inflammatory biomarkers acutely and following 3 and 6 weeks of isometric exercise training in two different exercising muscle groups.

The objectives for this aim are to:

1. Establish a relationship between IET induced reductions in RBP and the release of VEGF, TNF-a and IL-6 in human plasma.

2. Describe the influence of contracting muscle mass on IET induced reductions in RBP and the release of VEGF, TNF-a and IL-6 in human plasma.

I hypothesized that an acute session of isometric exercise will elicit selected blood factors into circulation when analyzed against baseline parameters. Additionally, I hypothesized that muscle mass trained (IBC vs. ILE) will be associated with the concentration of vasoactive factors (VEGF) and markers of inflammation (IL-6 and TNF-a) produced, along with reductions in RBP. Finally, I hypothesized that IET promotes a release of vasoactive (VEGF) and inflammatory biomarkers (IL-6 and TNF-a) at levels that correlate with proposed reductions in RBP.

Experimental Design and General Methods

Experimental Design

This dissertation was designed to address several limitations in the current literature with respect to age, cardiopulmonary disease, duration of training, the effects of detraining, efficacy of home-based training, and potential mechanistic variables (systemic blood biomarkers and muscle mass). Study 1 (Chapter 2) and 2 (Chapter 3) were developed to assess the chronic training effects of long duration IET programs with prolonged detraining protocol in two distinctly vulnerable populations (elderly adults, and cardiopulmonary rehabilitation patients). Study 3 (Chapter 4) was designed to investigate the efficacy of 12 weeks of home-based IHG vs. traditional laboratory-based exercise in adults diagnosed with HBP for future community-based engagement practices and to combat barriers associated with engaging in standardized exercise programming for HBP management. Study 3 was adapted based upon the limitations and pitfalls of study 1 and 2, which included recruitment, and retention of older adults and those with cardiopulmonary disease.

Studies 1-3 employed an identical and well-recognized IHG protocol for 12-weeks (see figure 8). Study 4 (Chapter 5) was a modified experimental design; with the aim of providing insight into mechanisms evidenced by training adaptations following 6-weeks of bilateral leg extension versus bilateral bicep curl isometric exercise at the same relative intensity. Furthermore, vasoactive (VEGF) and inflammatory (TNF-α and IL-6) biomarkers were assessed to explore the relationship between systemic biomarkers postulated to be involved in RBP adaptations following training. Secondarily, study 4 addressed muscle mass as a dependent or independent variable in responsiveness to IET. Figure 2. below illustrates the order in which studies in this dissertation were carried out.

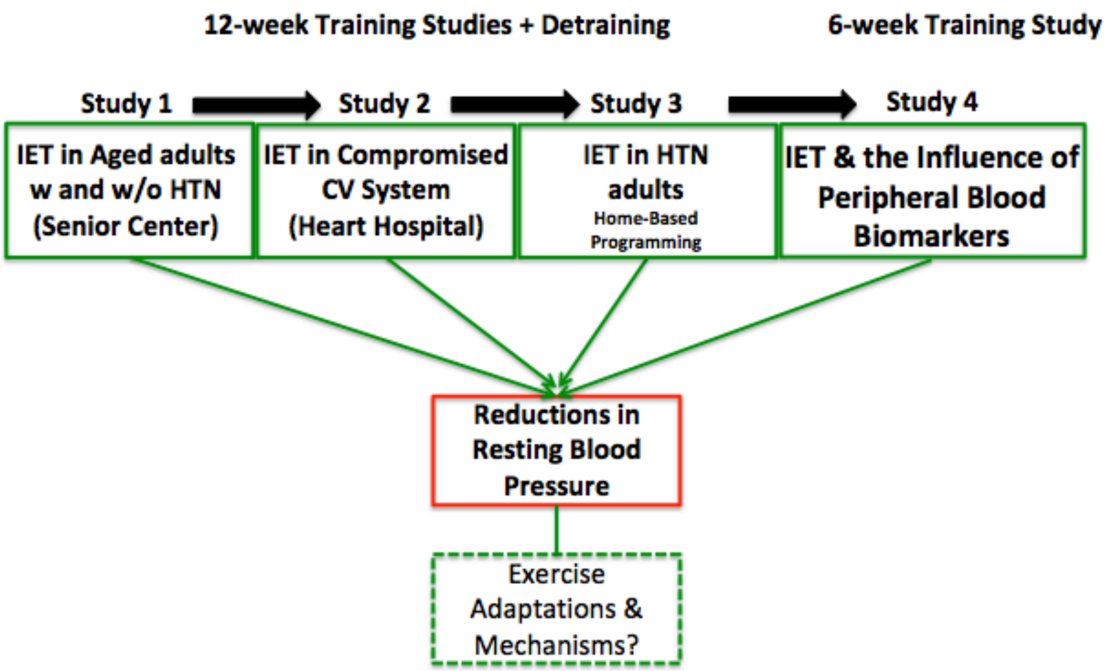


Figure 2: Schematic of the studies carried out in this dissertation

Study 1. Experimental Design:

The Tyvola Road Senior Center project was designed as a randomized observational study with two groups, control and handgrip (IHG) exercise. However, in order to remain in the study, recruited participants preferred choosing their respective study group in opposition to the randomized design. As a result study 1 became a non-randomized observational twelve-week handgrip study. Handgrip participants completed 4, 2-minute contractions at 30% maximal voluntary contraction (MVC) separated by 1-minute of rest, 3 days per week for 12-weeks. A 6-week and 12-week monitored detraining period was implemented at the end of training to address the potential for sustained reductions of BP in response to IET. The independent variables were group (IHG exercise and control) and time. Dependent variables include resting systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and heart rate (bpm).

Study 2. Experimental Design:

Study 2 was completed at Carolinas Healthcare Northeast Medical Center as a randomized controlled design with two groups; control and IHG exercise in adults diagnosed with cardiopulmonary and/or metabolic disease, and were current members of an outpatient cardiac rehabilitation program. Training participants completed the same exercise protocol outlined previously (see study 1 previously; Figure 8). However, due to recruitment and retention, along with attrition of participating subjects, data was collected and analyzed for 6-weeks with no detraining. This project was conducted in collaboration with Carolinas Medical Center (CMC), Northeast, an affiliate of the Sanger Heart and Vascular Institute, Concord, NC. The independent variables were group (IHG exercise and controls) and time. Dependent variables include resting systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and heart rate (bpm).

Study 3. Experimental Design:

Study 3 was a randomized controlled study with 3 groups; 1) Home-based (HOM) IET, 2) Lab-based (LAB) IET, and 3) a control (CON) group. IET exercise participants (both HOM and LAB) utilizing the protocol outlined previously (see study 1 previously; Figure 8). This study utilized a video-based delivery platform for HOM exercise. Two short videos were filmed in the home simulation lab at UNC-Charlotte. YouTube was chosen to for dissemination of IET outside the laboratory. This study was designed with the intent of targeting convenience and cost effectiveness of home or workplace IET. The independent variables were group (HOM IET, LAB IET, and CON) and time. Dependent variables include resting SBP (mmHg), DBP (mmHg), HR (bpm), and exercise adherence (# of sessions).

Study 4 Experimental Design:

Study 4 was a randomized controlled trial that included 3 groups; 1) bilateral bicep curl (IBC) IET, 2) bilateral leg extension (ILE) IET, and 3) a control group. IET participants (IBC & ILE) completed a modified protocol; Based on a review of the literature study 4 was adapted from Howden et al. [2002] and Gill et al. [2015]; Authors described the difficulty maintaining 20-30% double leg extension and 30% double arm curl for 2-min bouts repeated 4 times. This protocol was modified to achieve an equivalent volume of IET relative to previous investigations but carried out incorporating an intensity that could be maintained consistently during each exercise session. The modified protocol included 6 x 2-minute contractions at 15% MVC, separated by 1-

minute of rest, 3 days per week for 6 weeks. The independent variables were group (IBC IET, ILE IET, and controls) and time. My dependent variables were resting systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (bpm), plasma VEGF (pg/mL), IL-6 (pg/mL), and TNF-α (pg/mL).

Participants

Participants (n=77) were recruited and took part across the 4 studies in this dissertation. While this dissertation revolves around the central theme of IET, prospective participants were recruited relative to each study question and are described in detail below. The University of North Carolina at Charlotte's Institutional Review Board (IRB) and Office of Biosafety approved the following studies unless otherwise specified (i.e. study 2, The Carolinas Healthcare System IRB approved the study).

Study 1.

Participants (n=24) were identified as males and females 55 years and older and active members of the Tyvola Road Senior Center in Charlotte, NC. Prior to their involvement all participants were presented with a study information sheet and informed consent document. Participants first read and then signed an informed consent before any questionnaires, training, or testing procedures were completed. Individuals with physical impairments preventing them from performing IHG exercise or maximum handgrip contractions (e.g. age-related neurological diseases) or BP ≥160/100mmHg were excluded from this study. Participants completed a Physical Activity Readiness Questionnaire (PAR-Q) and had their resting blood pressure taken to determine if they were eligible for the study.

Participants were then randomly allocated to one of two study groups; class-based IHG or control. As stated briefly, such was the enthusiasm for participation in the study several participants randomized to the control group indicated their involvement would be contingent upon being allowed to participate in IHG sessions with fellow senior center patrons. During enrollment all participants were encouraged to maintain their regular exercise, diet, and medication regimens for the duration the study. All recruited participants had to speak sufficient English to understand the details of the study including how to participate in IET. Furthermore, participants were provided an individual participant journal where they were asked to record unavoidable life changes or health consequences and were asked to report them to the primary investigator during weekly meetings. Participants received training on all equipment and detailed procedures were explained to all participants prior to the start of exercise and testing.

Study 2.

Participants (n=11) were defined as past, current, and future patients of Carolinas Medical Center Northeast Cardiovascular/Pulmonary Rehabilitation. Prior to their involvement all participants were presented with a study information sheet and informed consent document. Participants included but were not limited to post operative/ percutaneous coronary intervention, stent placement, diagnosed cardiopulmonary disease, metabolic disease, and those without specific intervention including non-ischemic heart disease patients.

Inclusion criteria included; cleared for exercise by the patient's physician or cardiologist and a past, current, or future patient of Heart Success and/or Cardiac/Pulmonary Rehabilitation at CMC Northeast. Exclusion criteria included not being cleared for exercise by the patient's primary care physician or cardiologist and/or not a past, current, or future patient of Heart Success and Cardiac/Pulmonary Rehabilitation at CMC Northeast. All recruited participants had to speak sufficient English to understand the details of the study including how to participate in IET. Training of equipment and detailed procedures were given to all participants prior to the start of exercise and testing. The Carolinas Healthcare System Institutional Review Board approved the study.

Study 3.

Participants (n=25) were hypertensive (>130/81 but <160/100 mmHg) males and females (21-65 years of age) when measured by the investigators prior to enrollment or were currently being treated for HBP with prescribed antihypertensive medication for at least 6-months prior to enrollment. Participants were provided an informed consent prior to any involvement in the study. All participants were graduate students, faculty, or staff of UNC-charlotte for the duration of their enrollment in the study. Inclusion criteria further included those who were physically able to perform maximum muscle contractions with their hands without extreme discomfort (based on health history questionnaire); potential subjects must also have spoken sufficient English; not currently pregnant nor become pregnant during the study period; and understand fully the details of the study including how to participate in IET.

Study 4.

Prior to their involvement all participants (n=17) were presented with an informed consent document. Participants were male, UNC-Charlotte undergraduate or graduate students; at least 18 years of age; English speaking; absence of physical limitations in the legs or arms that would prevent a potential participant from completing these exercises; a resting blood pressure <130 mmHg systolic/ <81 mmHg diastolic but > 90 mmHg systolic/ >70 mmHg diastolic; taking no prescription or over-the-counter medications that influence cardiovascular activity, have mood altering or anti-inflammatory effects (e.g., beta blockers, anti-hypertensive, psychostimulants, steroids, anti-cytokines, anti-depressants, sedatives, anti-psychotics, high dose non-steroid anti-inflammatory drugs); diagnosed with any chronic health conditions (e.g., diabetes, cardiovascular disease, autoimmune disorders, cancer, high blood pressure); and spoke sufficient English to understand instructions about performing IET.

Exclusion criteria for study 4 were detailed and were more stringent due to the inclusion of blood analyses. If the following variables had been included, they may have contributed to increased variation in our sample as several are known to influence inflammation (e.g. smoking and high dose inflammatory medications) and may have potentially masked or inflated results. Exclusion criteria included not a male; not a UNC Charlotte undergraduate or graduate student; under 18 years of age; anyone with resting blood pressure higher than 130/81mmHg or lower than 90/70 mmHg; anyone with an injury or physical characteristic that would have prevented them from doing isometric exercises; smokers of tobacco products and marijuana as well as the use of illicit drugs like heroin, cocaine, methamphetamine, ecstasy, LSD, hallucinogens or their derivatives or abused prescription drugs in the past 12 months; currently experiencing an acute illness or infection; currently taking medications or supplements that may affect or influence inflammation [i.e., high dose non-steroidal anti-inflammatory drugs (800 mg/day Ibuprofen or 1250-1375 mg/day Naproxen) for up to 10 consecutive days, and steroid medications]; current diagnosis or personal history of significant cardiovascular complications (i.e., hypertension, congenital heart disease or disorders, cardiovascular disease such as heart attack or stroke), or current use of blood pressure lowering medications; current diagnosis of inflammatory diseases and disorders (i.e., asthma, diabetes, obesity, autoimmune disorders, cancer, major depression, cardiovascular disease, celiac); a surgery in the past 3 months; and/or were unable to understand the informed consent document.

If an active participant presented with an elevated blood pressure outside the study inclusion or exclusion parameters they were asked to return for another blood pressure a day later for validation to confirm that the previous measure was not an error. If the pressure was still high (elevated, >20% compared to baseline), participants were terminated from the program, and in the event those values exceeded safe guidelines SBP >160 or DBP >100 mmHg participants were encouraged to seek medical advice from a medical professional.

Participant Recruitment

Study 1.

Recruitment took place onsite at the Tyvola Road Senior Center. Along with posted flyers, members of the research team approached potential participants and invited them to participate. The recruitment period for study 1 took place in the fall of 2013. Following the recruitment period the study commenced on site with participants in the spring of 2014.

Study 2.

Because recruitment took place in a hospital environment and in accordance with the rules and regulations set forth by health insurance portability and accountability act (HIPAA); members of the research team were not allowed to initiate communications with potential study participants. Current members of the treatment team (medical Staff) presented the study to prospective participants that had been designated as "cleared for exercise" by the patient's primary care doctor or cardiologist. The treatment team explained the collaboration between Carolinas Medical Center and UNC Charlotte, speaking directly to the goals and aims of the study. Additional recruitment was made via posted flyers on site in the cardiac rehabilitation suite. A copy of the recruitment flyer can be found in Appendix 2.

Had the patient expressed interest they met with members of the research team whereby a formal demonstration by the principal investigator was given. Had participants remained interested they attended an orientation session meeting one on one with study team members. All participants were selected based on willingness to volunteer for the study. Each participant had a 50/50 chance of being selected for one of the two designated groups (IET exercise and Control). Recruitment for the study took place over the course of 1 month. The principal investigator first met with cardiac rehabilitation participants in the fall of 2015 and the study spanned a 6-month period into the spring of 2016.

Study 3.

Participants were recruited through the use of campus fliers and via university mass email system. The university IT department identified potential participants meeting basic inclusion parameters (University status and age). Interested individuals contacted members of the research team via email and were screened for inclusion and exclusion criteria by phone. See Appendix 3 and 4 for a copy of the screening questionnaire and campus recruitment flyer. Finally, participants in each of the groups (LAB, HOM, and CON) were incentivized to participate and had the chance to win a $100 gift card at scheduled data collection time points (i.e. 1 in 20 chance at each of 4 time periods). At the final data collection point, each member was entered for a chance to win a new handgrip dynamometer identical to those used in the study.

Study 4.

Participants were recruited through research team presentations given in the department of Kinesiology at UNC-Charlotte and via the university mass email system as previously described. Recruitment email language can be found in Appendix 7.

Interested participants contacted the research team via email. The investigator then administered over the phone eligibility screenings. Questions for screening were detailed, thorough and sensitive in nature, as such, the author did not record results of the screenings but deemed participants eligible or ineligible, without specification (a copy of the screening questionnaire can be found in Appendix 8 and in the preceding section Participants – Study 4). Following the screening process eligible participants were invited to the Laboratory of Systems Physiology to undergo a resting blood pressure assessment. If participants remained eligible they were invited to participate and provided an informed consent document for review. Once the informed consent document had been signed participants were randomly allocated to one of three research groups.

Finally, participants were incentivized to partake in the study ($75). Eligibility for compensation included; subject must have completed at least 80% of exercise sessions and 100% of blood draws. A participant who withdrew and/or do not complete a minimum of 80% (exercise) and 100% (blood draws) of the study were not eligible for gift cards.

Instrumentation and Procedures

Camry Handgrip Dynamometer

The Camry 200lb EH101 handgrip dynamometer (Figure 6a) was selected for studies 1, 2, and 3. This device was used for daily MVC determination and 3x weekly exercise sessions. This device is equipped with a high precision strain gauge sensor and is engineered for accurate measurement of handgrip strength and has been used in physician and physical therapy offices, engineering labs, and gyms. When the participant squeezes, the dynamometer registers real time handgrip strength providing a digital readout that can be used for establishing exercise intensity for that day. Moreover, the device is a cost effective option ($29.99 USD) for assessing handgrip strength and administering IHG training. The device is adjustable and can be personalized to the hand size of participants for an individualized exercise session.

The device runs on 2 AAA batteries, which were provided by the research team and at no cost to participants. The Camry 200lb dynamometer provided real time quantifiable evaluation of contraction strength and was easy to use and transport. Through the hard work by Ms. Emily Zacherle (via self-initiated Crowd Funding) and Ms. Sarah Whitmire (Research Support through the Levine Scholars Program) our lab was able to purchase more than 80 individual handgrip devices for use in our lab and for future community-based interventions. For their dedication the author and laboratory are extremely grateful.

Biodex Isokinetic Dynamometer- System 4-Pro

The Biodex® System 4-Pro was used in study 4 only for this dissertation. This device is well recognized in physical therapy offices and research facilities. The equipment provides consistent and accurate results for evaluating strength and resistance capacity of upper and lower extremities and is considered a 'Gold Standard' in rehabilitative medicine. Moreover, this device can be modified to accommodate participants of varying stature. Adjustments to the seat height, chair slide, and attachment length allowed investigators to accommodate each individual participant in order to obtain the most accurate results possible.

Per the specification of the equipment the Biodex® software allows investigators to establish a fixed position of the movement arm based on the protocol design by the author. For this study, 90° was selected for both upper and lower body IET. Biodex® software registers torque produced in newton meters (Nm), which can be converted to foot-pounds (ft-lb). IET participants in study 4 performed 15% of MVC in Nm. The following conversion factor provided by Biodex® can be used to convert Nm to a more measurable parameter of mass, kilograms, in line with that of studies 1-3. This measure can be used to aid participants in quantifying intensity of the exercise during each exercise session and may be incorporated using other equipment in future studies.

Conversion formula: MVC (kg) = Nm → ft-lbs (2.6181) = lbs. / 2.2
65 Nm (0.737 ft-lb) = 47.94 X 2.6181
125.51 lbs. / 2.2 = 57.05 kg

Modification of Biodex® Attachment Components for Bilateral Limb Exercise

Due to the limitations of unilateral limb exercise; manufactured attachments were modified to accommodate bilateral exercise. See Figures 4 and 5 for representative images of modified Biodex® attachments in order to enable research participants in study four [see chapter 5] to engage in bilateral leg extension or bilateral arm curl exercise. A detailed description of each modification is provided in the proceeding section MVC Contraction Force and Isometric Exercise. The author is extremely grateful for the guidance and skilled expertise of the dissertation committee chairperson, Associate Professor Dr. Reuben Howden (The University of North Carolina at Charlotte) during the design phase of this study.

Automated Oscillometric Blood Pressure Assessment

In all 4 studies (chapters 2,3,4 and 5) the American Diagnostic Corporation Adview 9000 automated sphygmomanometer was utilized. Our investigations aligned with currently prescribed guidelines for appropriate blood pressure assessments [Pickering, 2003; Pickering, 2005; Ogedegbe and Pickering, 2010; see section. Methods for Measuring for detailed guidelines]. Friz et al. [2009] confirmed the accuracy of the Adview 9000 for clinical use, and met requirements for 'A' grade classification for measurement of both SBP and DBP measures.

All blood pressure assessments were completed at approximately the same time for each collection (within 1hr). Measures were collected twice in a single session separated by 5 minutes. An average of the two measures was used for analysis at each weekly time point. In the event that measures were greater than ~10-15 mmHg in study

1-3, and greater than ~5-7mmHg in study 4 from one another a third measure was collected and evaluated against the first two measures.

The BP cuff was placed on the non-dominant arm following a circumferential measurement per participant for accuracy [Pickering, 2003]. Before measurements participants rested quietly for 15-minutes in a temperature controlled room in the seated position, with their legs uncrossed and feet flat with the arm at heart level [Pickering, 2003; Pickering, 2005; Ogedegbe and Pickering, 2010].

Prior to collection all participants were asked to do the following:

- Refrain from caffeine consumption 12 hours before
- Refrain from alcohol consumption 12 hours before
- Consume only water, 2 hours before
- Avoid vigorous physical activity outside of a normal routine 24 hours before
- Void their bladder before testing

The only variation in the evaluation blood pressure took place in study 4 (chapter 5). Whereby investigators, in an attempt to account for white coat HTN and/or familiarization induced reductions blood pressure, extended the baseline pre-intervention period (3 weeks, see chapters 1 and 5; Methods for Measuring Blood Pressure).

An extended baseline period allowed the author to establish a more accurate RBP. In studies 1-3 a total of 6 pre-intervention blood pressures were collected; in study 4 a total of 27 pre-intervention RBPs were completed. Furthermore, all measures were withheld from participants until the end of the training period in study 4 only. At the conclusion of study 4 researchers provided full disclosure of collected data to each individual subject at their request. Unless otherwise specified all protocols and procedures required of participants for blood pressure assessments were identical across each study.

Procedure for collection of blood samples (venipuncture)

The Laboratory of Systems Physiology, the University of North Carolina at Charlotte guidelines for sampling and handling of blood samples were adhered to for the collection of all blood samples. A certified phlebotomist collected 10mL of blood from the brachial vein via the antecubital fossa of the non-dominant arm of each participant regardless of study group at specified time points (see study 4 chapter 5 for detail). All blood draws took place at the same time of day per participant within 1 hour of baseline measures. A non-latex tourniquet was affixed to the participant's non-dominant arm while in the seated position. The draw site was prepared with a 93-96% alcohol swab, cleansing and cleaning to reduce likelihood of infection. After the site had dried, the subject had a standard 21G Vacutainer blood collection needle (BD Vacutainer® Eclipse™) with pre-attached holder inserted into the brachial vein. Venous blood was drawn into 10mL EDTA tubes (BD Vacutainer® US) and immediately underwent centrifugation at 2000 x g for 15 min at room temperature [Sample Processing and Storage Guidelines, University of Virginia School of Medicine, 2018].

Blood draws were performed 9 times over the course of the study period with three draws at 0, 3, and 6 weeks of training respectively. Regardless of group all blood was collected following a fasted 12 hours. All blood draws were taken at the same time of day per participant within 1 hour of the initial draw.

Upon sample collection, the needle was disposed of using appropriate biohazard safety materials (puncture proof biohazard sharps containers and red biohazard bags.

Participants were provided cotton balls/ gauze following blood draw to stop bleeding at the puncture site. A non-latex bandage was applied to the site. All soiled materials, including gloves, gauze, cotton balls were disposed of as appropriate following protocols established and approved by the Office of Biosafety.

Meso Scale Diagnostics (MSD) V-Plex Electrochemiluminescence (ECL)

MSD assays provide for rapid and convenient method for determining levels of protein targets using a small volume sample (~25μl). These assays act under the same principle of the commercially available sandwich ELISA assays. MSD Plates were ordered and arrived pre-coated with capture antibody on pre-defined spots relative to protein of interest (VEGF, IL-6, TNF-α).

In collaboration with the Department of Psychological Sciences the QuickPlex SQ120 (#AI0AA-0 Mesoscale Diagnostics, Rockville MD) was used for analysis of both vasoactive and inflammatory biomarkers. With this instrument up to 10 analytes could be analyzed per well simultaneously. Within the limitations of this dissertation we analyzed up to three analytes simultaneously. MSD is recognized for rigorous control protocols and validated testing in their kits. Plates are highly sensitive, simple, and reproducible for successful quantification of analyte per sample.

For analysis the sample (plasma) was added to each well and underwent an initial 2 hr. shaking incubation period to allow the analyte (VEGF, IL-6, TNF-α) to conjugate with the capture antibody. Following, a series of plate washes were completed (x3) and MSD SULFO-TAG electrochemiluminescent labels were added. A second 2 hr. incubation period with shaking, conjugated and completed the sandwich. After a final series of washes (x3) an MSD buffer was added creating an ideal chemical environment for electrochemiluminescence. The plate was then loaded into the SQ 120 instrument for analysis. Once the plate was placed in the instrument, voltage was applied by the working electrode affixed to the bottom of the plate. Voltage causes the captured SULFO-TAGs to emit light. Detection occurs via the Cooled Scientific-grade CCD camera with precision lens. The SQ120 (#AI0AA-0) measures the intensity of emitted light, which is proportional to the concentration of analyte present in the sample and is then converted to representative unit relative to the biological concentration for analysis. The following are specific upper and lower limits, intra-run %CV and intra-lot % CV pertaining to each assay per analyte.

Table 1. VEGF: LLOQ, ULOQ, intra-run and intra-lot % CV for each analyte.

	LLOQ (pg/mL)	ULOQ (pg/mL)	Intra-run %CV	Intra-lot % CV
			2.3	6.7
VEGF-A	7.70	562	2.4	7.8
			3.4	7.2

Table 2. IL-6: LLOQ, ULOQ, intra-run and intra-lot % CV for each analyte

	LLOQ (pg/mL)	ULOQ (pg/mL)	Intra-run %CV	Intra-lot % CV
			3.6	4.2
IL-6	1.58	488	3.9	5.1
			4.5	5.5

Table 3. TNF-α: LLOQ, ULOQ, intra-run and intra-lot % CV for each analyte

	LLOQ (pg/mL)	ULOQ (pg/mL)	Intra-run %CV	Intra-lot % CV
			2.7	7.2
TNF- α	0.690	248	2.4	6.3
			3.4	6.2

LLOQ: lower limit of quantification; ULOQ: upper limit of quantification; CV: coefficient of variation; VEGF: vascular endothelial growth factor; IL-6: interleukin-6; TNF-α: tumor necrosis factor alpha.

Maximal voluntary isometric contraction force and isometric exercise

In studies 1-3 MVC was determined using a Camry handgrip dynamometer as previously described. MVCs were completed using the flexor muscles of the forearm and hand of the self-selected dominant upper extremity for exercise prescription. Participants were required to perform three MVCs, each separated by 1-minute of rest that were not different by more than 20% (e.g. 40±8 kg). The maximum force produced from the MVC test was used to calculate the isometric exercise intensity for their exercise session that day.

In study 4 MVC was determined using an isokinetic dynamometer as previously described (Biodex® System 4 Pro) with participants suitably restrained (Figure 4). For the leg condition the leg extension attachment was modified by sliding a length of 50mm square steel tube, with 5mm wall thickness, over the single leg Biodex® attachment and secured in place with 4 setscrews. The commercially available right and left leg extension/flexion attachments were then both affixed to the steel tube, enabling participant to perform bilateral isometric exercise using both legs. Double leg MVCs were performed by contracting the extensor muscles at a knee joint angle of 90°. Participants were required to perform three MVCs separated by 15 seconds. The maximum force produced from the three MVCs was used to calculate isometric intensity for that session [see conversion formula described previously].

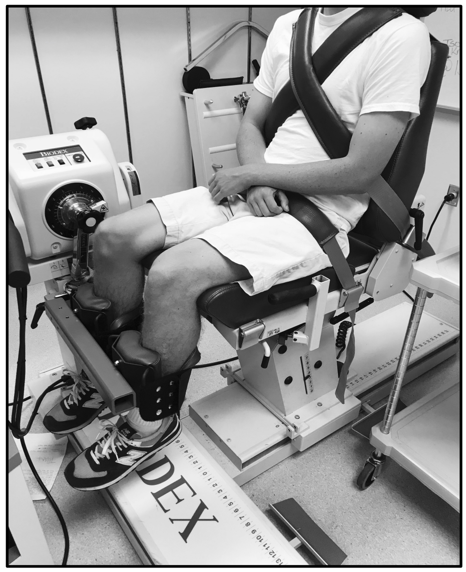


Figure 3: Depicting the modified single limb knee extension/flexion attachment for bilateral knee IET.

For subjects completing bilateral arm curl exercise MVC was determined using the same Biodex isokinetic dynamometer with subjects suitably restrained (Figure 5). As with leg exercise a bilateral attachment is not available using standard equipment. Therefore, the author pieced together the left forearm grip attachment at its end to the "foot rest" attachment inverted to create a modified bilateral arm curl bar. This bar was long enough and allowed for subjects to use both arms to complete exercise sessions. Further, in order to complete arm curl exercise appropriately an armrest was custom designed and built to fit within the existing stabilization handles of the equipment. Three lengths of 25mm square steel tube with a wall thickness of 1.6mm were welded to form a three-sided rectangle to fit in pre-existing attachment points on the Biodex®. MVCs using the arms were performed by contracting the elbow flexor muscles at an elbow joint angle of 90°. Prior to all MVC's the author measured with a goniometer both knee joint and elbow joint angle to ensure subjects were exercising appropriately angle for the duration of the study.

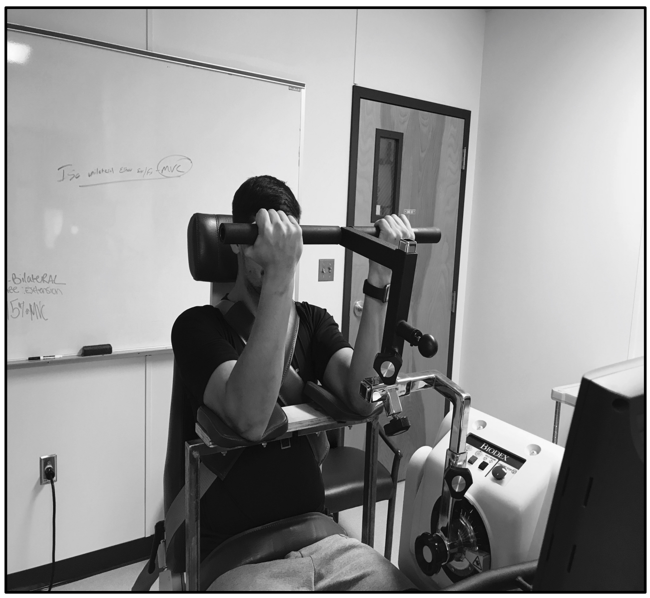


Figure 4: Depicting the modified single limb elbow flexion/extension attachment for bilateral arm curl IET.

The isometric exercise training protocol used in studies 1-3 followed a protocol used often in the IET literature [Lawrence et al. 2014; Millar et al. 2014]. In each exercise session 4, 2-minute bouts of isometric exercise were performed by subjects at 30% MVC. Each 2-minute bout of exercise was separated by 1-minute of rest (see Figure 8 for IHG protocol design).

The IET protocol used in study 4 was a modified version of the protocol used in studies 1-3. 20-30% of MVC of double leg or arm exercise is a difficult intensity of exercise to perform adequately [Howden et al. 2002; Gill et al. 2014]. Intensities that incorporate a larger volume of muscle mass (IBC and ILE) would be more difficult for participants to maintain adequately across 6 bouts [Howden et al. 2002; Gill et al. 2014]. Therefore, lower intensities but still within an anti-hypertensive range (10-30%) is more realistic for broad population use. The author chose to adapt the protocol published by Howden [2002] and Gill et al. [2014] where in each exercise session 6, 2-minute bouts of isometric exercise were performed at 15% of MVC. Each 2-minute contraction was separated by 1-minute of seated rest.

Home-Based Video Preparation

In study 3, home-based isometric exercise was designed for successful completion in an environment of the participants choosing. A Certified Exercise Physiologist with experience administering IET protocols and the other a Certified Health Education Specialist with public health intervention expertise collaborated to create the instructional isometric exercise training videos. Video extras included a group of diverse graduate students from the Universities' Department of Kinesiology all with experience at completing IET procedures. Videos were filmed utilizing the Home-Simulation Lab onsite at the University of North Carolina at Charlotte.

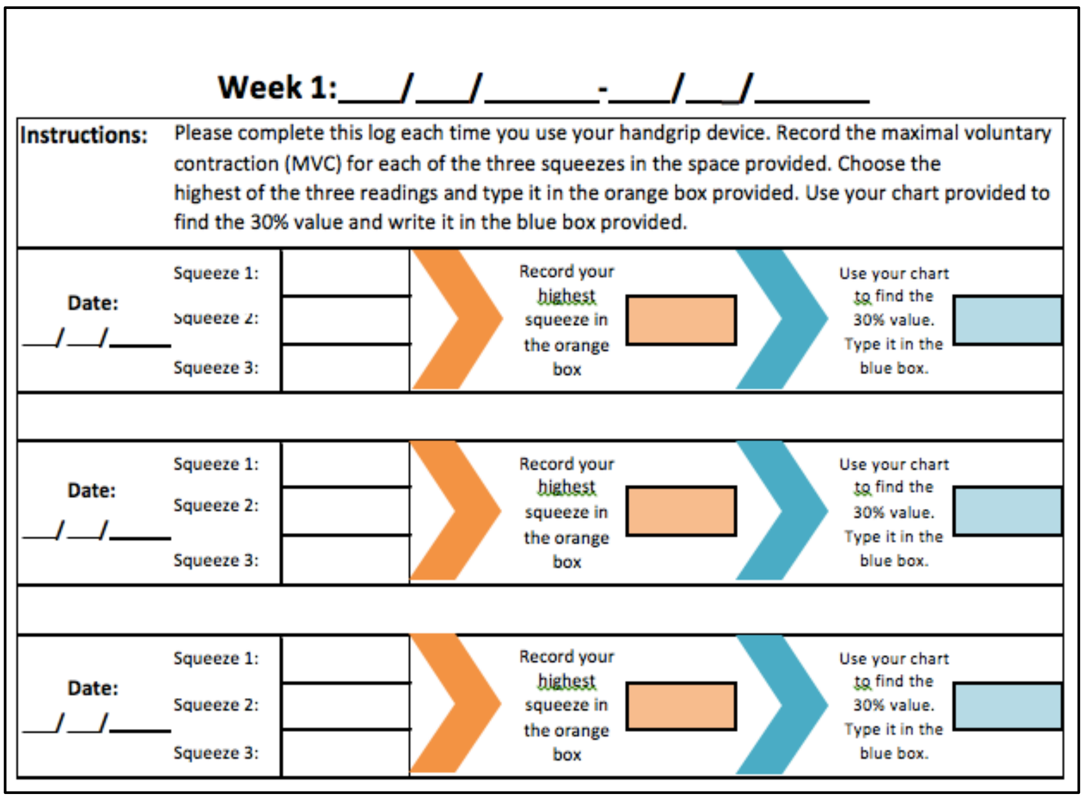
Two instructional videos were used for home programming. Video 1, included a short (<5 minutes) segment about the benefits of IET on blood pressure and what participants should expect to experience during IET sessions, which was designed for participants to watch just once during their first session. The second video was a step-by-step, timed instructional video guiding participants through the IET protocol (see video links below). Participants were encouraged to watch the second video each time they completed a home IET session. The videos were accessed through a private YouTube link to which only the research team and participants could view. In the event a home-based IET subject was unable to watch the videos via YouTube, detailed step-by-step written instructions were also provided in the HOM participant packet. Exercise video links and captured stills from each of the training videos can be found below. A detailed description of the home-based exercise instructions can be found in Appendix 6.

Figure 5a: Video still depicting home-based IET MVC instruction, prior to 3x weekly IHG sessions

Figure 5b: Video still depicting home-based (HB) IHG completed to 3x weekly for 12-weeks

Home-Based Participant Tracking

In study 3, home based exercise participants were asked to track their participation using the weekly exercise log [Figure 7]. This packet was broken into several sections, which were outlined in Video 2. Investigators provided step-by-step instructions for completion of the exercise log including each record of MVC (#1-3), highest MVC, and then calculated 30% MVC measure obtained from the conversion table, also provided (see Appendix 6)


Week 1:___/___/_______-___/___/_______

Instructions: Please complete this log each time you use your handgrip device. Record the maximal voluntary contraction (MVC) for each of the three squeezes in the space provided. Choose the highest of the three readings and type it in the orange box provided. Use your chart provided to find the 30% value and write it in the blue box provided.

Date: ___/___/____ | Squeeze 1: / Squeeze 2: / Squeeze 3: | Record your highest squeeze in the orange box | Use your chart to find the 30% value. Type it in the blue box.

Date: ___/___/____ | Squeeze 1: / Squeeze 2: / Squeeze 3: | Record your highest squeeze in the orange box | Use your chart to find the 30% value. Type it in the blue box.

Date: ___/___/____ | Squeeze 1: / Squeeze 2: / Squeeze 3: | Record your highest squeeze in the orange box | Use your chart to find the 30% value. Type it in the blue box.

Figure 6: Home-Based (HB) IET participant tracking packet. Sheets were completed for all IHG: isometric handgrip session's weeks 1-12 of exercise.

Outcome measures

All outcomes measures have been previously described. Within this dissertation the following variables were measured and analyzed relative to the study question in each study. Resting blood pressure (SBP, DBP), Heart Rate (HR), MVC, VEGF, IL-6, and TNF-α.

Testing protocols

Testing protocols in study 1-3 and 4 have been described previously in brief. A representative figure of the protocol used in our lab for studies 1-3 and 4 can be found below respectively (Figures 8 and 9).

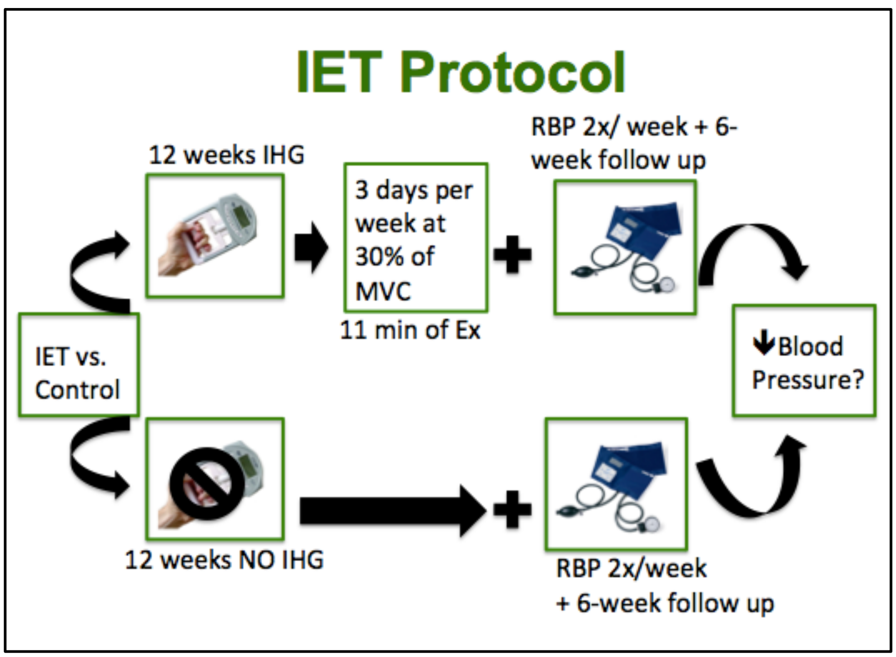


Figure 7: Representation of the standard IHG protocol implemented in the Laboratory of Systems Physiology. This protocol was employed in studies 1-3 for IHG exercise 3x/ week for up to 12-weeks

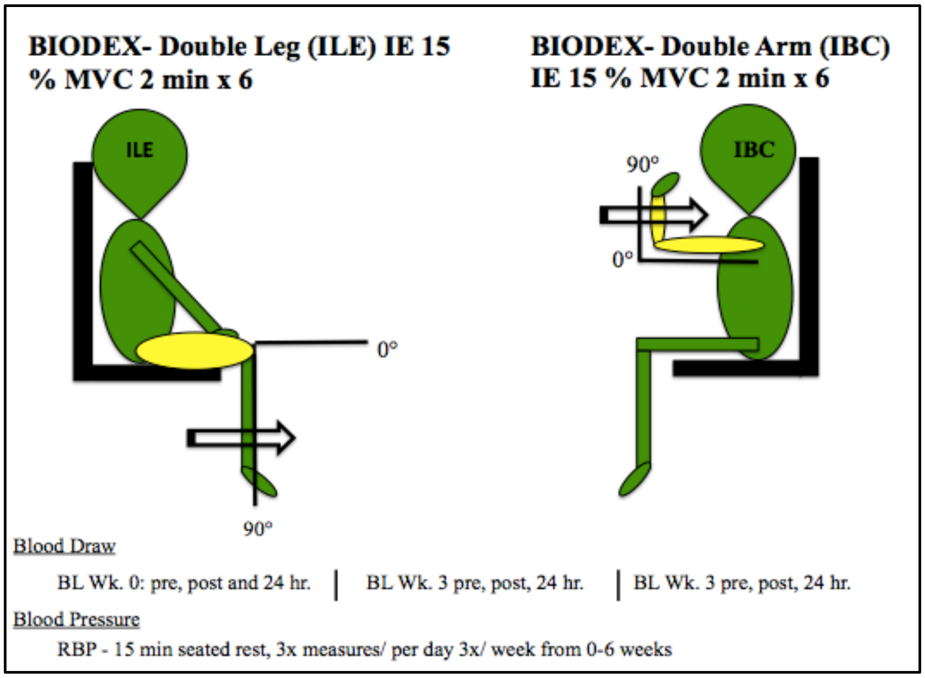


Figure 8: Representation of modified IBC vs. ILE protocol implemented in the Laboratory of Systems Physiology. This protocol was employed in study 4 for IET 3x/ week for 6-weeks.

Statistical Analyses

Study 1-4**.** All RBP For RBP, to assess trends in SBP and DBP across the six-12 weeks of training among the treatment groups, we calculated two measures. One measure was obtained by regressing BP values (dependent variable) on weeks (independent variable) for each individual in all treatment groups (2-3 relative to study). Preliminary tests of the slopes of these regressions were conducted to assess linearity, with no curvilinear trends ($P > 0.05$). We obtained a second measure for each individual by subtracting the participants BP at the end of the trial from the initial BP taken before the treatments started.

We then tested for potential differences in the means of the regression coefficients and of the BP differences among the treatment groups using an analysis of covariance (ANCOVA) model with treatment as a classification factor and the initial blood pressure of each individual as a covariate. We included the initial blood pressure of each individual (before treatments) in the model to adjust for any potential effects due to differences in this variable among the treatment groups. If preliminary tests showed that slopes of the blood pressure values on the covariate were parallel across groups ($P > 0.05$), we were able to proceed with a conventional ANCOVA. Linear regressions were used to analyze both whole group and individual trends in RBP over the course of 6 (study 2, chapter 3 and study 4 chapter 5) and 12-weeks (study 1, chapter 2 and study 3 chapter 4) of IET. The majority of the IET literature evaluates whole group mean changes in RBP. We conducted analyses in line with those previously and compared them. A 2 way ANOVA (time x intervention) with repeated measures was used to assess changes in RBP compared with pre-training measures. The Bonferroni post-hoc test was used for data that produces significant results and to identify specific differences.

Our expectation was that both measures of BP change for the control group would be near zero whereas they would decrease in the intervention groups, producing negative values. Because of this directional expectation, we halved the probability generated by the F tests in individual Dunnett's post-hoc tests of the differences in these measures in the control versus each of the two intervention groups. A significant ($P < 0.05$) result in either of these post-hoc tests (with the intervention groups, i.e. mean lower) was interpreted as support for our hypothesis that isometric exercise could reduce blood pressure.

Study 4. Analysis of blood markers was performed in slices for Control and each exercise group respectively; Control vs. HG, Control vs. SL, and HG vs. SL. An unpaired t-test was used to assess differences in baseline characteristics between groups. For each subject, each factor (e.g. VEGF) within each group a difference value was calculated at baseline, week 3, and week 6. A two way repeated measures analysis of variance (2 groups vs. two measurement points was (condition x time) for each of the blood factors. Interactions were assessed and if an F ratio was significant, post hoc analysis was made with sequential Bonferroni.

Power analysis

Previous investigations have identified significant differences in primary outcome variables (i.e. SBP, DBP, HR) when comparing pre and post exercise resting hemodynamic measures. With the assumption for significant heterogeneity in participant baseline RBP power calculations were conducted with an $\alpha = 0.05$; 0.10 and β set at 0.80. Sample size estimates and power calculations for studies 1-3 were determined using differences in SBP between control and IHG (effect size = 3-8 mmHg). The minimum sample size for a power level of 0.80 and a α=0.05 is 18 subjects per group with an effect size of 5 mmHg in SBP. The minimum calculated sample sizes for a power level of 0.80 and an α=0.10 is 14 subjects per group, with an effect size of 5 mmHg in SBP.

A table of calculated N to achieve statistical significance for effect sizes of 3-10 mmHg, α = 0.05-0.10, β = 0.80-0.95, is described in Table 1. Group differences have been observed in previous investigations with sample sizes of 10-20 participants per group and mean differences in RBP of Δ 10-14/6-8 mmHg when comparing pre and post SBP and DBP [Cornelissen and Smart, 2013;Kelley and Kelley, 2010; Owen et al. 2010].

However, Bartol et al. (IHG N=11; Control N=9) [2012] and Stiller-Moldovan (IHG N=13, Control N=12) [2012] did not observe significant differences in RBP between groups. Therefore it was the intent of the author to recruit 20 participants per group to allow for up to 25% attrition in our samples resulting in 15 participants per group.

Table 4. Calculated N per group with alpha (α) = 0.05-0.10 and beta (β) = 0.80-0.95 with calculated effect size mean difference in SBP of 3-10 mmHg.

Computed N per Group						
Index	Nominal α	Effect Size	Nominal β	Actual α	Actual β	Est. N
1	0.05	3	0.80	0.0500	0.804	47
2	0.05	3	0.95	0.0500	0.952	77
3	0.05	5	0.80	0.0498	0.811	18
4	0.05	5	0.95	0.0499	0.955	29
5	0.05	8	0.80	0.0488	0.817	8
6	0.05	8	0.95	0.0495	0.953	12
7	0.05	10	0.80	0.0476	0.842	6
8	0.05	10	0.95	0.0491	0.970	9
9	0.10	3	0.80	0.0999	0.805	37
10	0.10	3	0.95	0.1000	0.952	64
11	0.10	5	0.80	0.0996	0.807	14
12	0.10	5	0.95	0.0999	0.955	24
13	0.10	8	0.80	0.0979	0.859	7
14	0.10	8	0.95	0.0991	0.955	10
15	0.10	10	0.80	0.0952	0.863	5
16	0.10	10	0.95	0.0979	0.960	7

CHAPTER 2: RESTING BLOOD PRESSURE ADAPTATIONS TO 12 WEEKS OF ISOMETRIC EXERCISE TRAINING WITH 12 WEEKS DETRAINING IN AN ELDERLY POPULATION

The work in this chapter was presented at the American College of Sports Medicine Southeast Region Annual Meeting (2014).

Abstract

Purpose: Anti-hypertension management remains suboptimal. Elderly individuals are particularly affected by rising systolic blood pressure with increased age. The effectiveness of isometric exercise training (IET) in lowering resting blood pressure (RBP) has been reported previously, but not in older populations with comorbid conditions, for a prolonged training and detraining period. Methods: Participants recruited from a senior center (63-88yrs), completed IET at 30% maximal voluntary contraction (MVC), 3 days a week for 12 weeks. RBP was measured weekly during the training period and 12 weeks post-training. Results: 12 weeks of IET induced a significant reduction in systolic blood pressure (training -10.5±7.7mmHg; $P<0.05$) A sizeable, but non-significant reduction in RBP was observed in the control group (-4.5±6.9mmHg; $P>0.05$). This meant that the means were not statistically different between groups ($P=0.308$). 12 weeks after training ended, systolic blood pressure was still 9.4mmHg lower in the IET group compared to pre-training measures, with no significant change in the control group. Both negative and positive regression analyses indicated individual participant variation in responsiveness to IET. Conclusion: 12 weeks of isometric handgrip training induced a significant reduction in resting systolic blood pressure, suggesting that this mode of exercise training is an effective anti-hypertensive intervention in older individuals. In older participants, this reduction persists for a

significant length of time after training ends (12 weeks). However, individual variation in the effects of IET on resting blood pressure warrants further investigation to achieve maximum effectiveness in all participants, because outcomes are not uniform.

Introduction

Described in chapter 1. Age and Hypertension, prominent features of hypertension in the elderly include elevated SBP and a wide PP [Aznaouridis et al. 2016; Benetos et al. 1998; Burt et al. 1995; Hajjar and Kotchen, 2003;]. Therefore, an intervention strategy that successfully reduces SBP would decrease cardiovascular risk factors. Despite the documented success of IET there is a paucity of data regarding the effect of extended IET programs in the elderly and very limited information about the characteristics of detraining with regard to resting blood pressure (RBP). It is not clear if post-training reductions in RBP are more persistent if the training period is longer [see chapter 1, for a detailed discussion on the Effects of IET].

Other studies used IHG in young and older normotensive subjects, and found equivalent reductions in RBP [Badrov et al. 2013; Millar et al. 2008; Ray and Carrasco, 2000; Wiley et al. 1992]. Moreover, in older pharmacologically controlled hypertensive patients (51-74 years), SBP, DBP, and MAP were reduced after 10 weeks at 30% MVC, 3 days per week. SBP decreased approximately 8mmHg, and 83% of the training group participants experienced a reduction in DBP of ≥2mmHg [Badrov et al. 2013b].

We hypothesized that significant reductions in RBP would be observed following 12 weeks of IHG training in an elderly population and that these changes would be lost after 12-weeks of detraining.

Methods

Participants were recruited from the Tyvola Senior Center in Charlotte, North Carolina and gave written informed consent prior to enrollment in the study (chapter 2, Table 1). The University of North Carolina at Charlotte's Institutional Review Board approved the study. Our inclusion criteria required that participants were at least 55 years of age, able to perform maximum handgrip contractions and had a resting blood pressure of less than 160/100mmHg. All participants were encouraged to continue their normal exercise routine, diet and medications throughout the study, but reported any unavoidable alterations (e.g. changes in medications health and illness). All participants were asked to abstain from consuming drinks and food, except water, 2 hours prior to any testing or exercise.

Procedures

Recruited participants were randomly assigned to either IET, in which exercise classes were held at the center 3 days per week or Control (CON). After an initial orientation and procedures familiarization session, subjects began IET. Weekly pre-measure questionnaires were given to account for caffeine use, fasting, and to ensure medications had been taken at their prescribed time and dosage, before each measurement. A Physical Activity Readiness Questionnaire (PAR-Q) was administered every 6 weeks throughout the study to account for any changes in diet, medications, physical activity, and/or health status.

Resting Blood Pressure and Heart Rate Measurements

An automated BP monitor (American Diagnostic Corporation Adview®9000, Hauppauge, NY) was used to measure weekly, at the same time of day, RBP and HR after 15 minutes of seated, quiet rest [Pickering et al. 2003]. A BP cuff was placed on participants' non-dominant arm, with the arm supported and at heart level. Measurements were made twice in one sitting, separated by one minute. An average of the two values was used as the subjects' weekly RBP and HR measurements. A third measurement was made if the second measurement differed from the first by 20% or more. For two weeks prior to the start of group exercise classes, RBP and HR were measured, and the average of these measures was used for baseline RBP and HR.

Maximum Voluntary Contraction Assessment

A Takei digital handgrip dynamometer (T.K.K 5401; Takei Scientific Instruments CO., LTD.) was used to accurately measure participants' maximum voluntary contraction (MVC) once every 6 weeks throughout the study. Participants performed MVCs while seated, in both hands (separately); shoulder adducted, elbow bent, with arm and hand resting in their lap while holding the dynamometer. All MVCs and handgrip IET were performed in this position. Participants performed at least three (no more than five) 2-second MVCs, each 60 seconds apart, which were not different by more than 20% (described previously, see chapter 1 Methods). Prior to each exercise session, the IET group measured their own MVC (dominant hand only) using a personal handgrip dynamometer (Camry 200lb Handgrip Dynamometer, City Industry, CA) provided for them at the beginning of the study. Participants used the same dynamometer that was assigned to them for all 12-weeks of training. After determining their MVC, a note card was given to participants with their 30% MVC workload for them to reference during contractions.

Exercise Training Classes

IET group participants exercised three days per week (Monday, Wednesday, and Friday) on site at the senior center. Participants performed 2-minute contractions at 30%MVC using their dominant hand, completing 4 reps, with 1 minute of rest in between (see chapter 1. Methods for establishing an MVC and the IHG protocol Figure 8.). Each exercise session lasted less than 15 minutes. Research staff provided support and oversaw participants during exercise to ensure (i) they were maintaining the appropriate workload for all contractions and (ii) not experiencing undue discomfort.

Detraining

RBP was monitored weekly after cessation of training for 6 weeks (week 18). A final RBP measurement was recorded 12 weeks after cessation of training in 13 handgrip exercise group participants and 5 control participants (week 24).

Statistical Analysis

All data were analyzed using SAS statistical software and graphpad prism software. Initially designed for randomized allocation groups, we altered the study design where those participants were allowed to self-allocate to the exercise group if preferred. Initial analyses included a 2 way ANOVA [time X training intervention (exercise versus a control condition)] with repeated measures that was used to assess changes in RBP and HR compared with pre-training measures. The Student Newman-Keuls post-hoc test was used for data that produces significant results and to identify the significance of specific differences. Secondarily, to test differences between groups and due to heterogeneity in baseline resting blood pressure that was to be expected, we tested for individual regression coefficients using a general linear model (GLM). Mean regression coefficients for each group were calculated and then analyzed. Linear regressions were used to analyze both whole group and individual RBP over the course of 12-weeks of IET. We tested for treatment x time interaction within and between groups, and the alpha level was set at $p<0.05$.

Results

Participants

No significant differences were found between groups in age, body mass, BMI or height (Table 5.). These participant characteristics were not associated with blood pressure adaptations observed in this study. Moreover, although some participants found 30% MVC handgrip isometric contractions a challenge at first, all participants were able to maintain the required intensity of exercise training and 83% of IET sessions were completed on average (30 of 36 sessions) None of the participants completed 100% of their exercise sessions. The highest completion rate was 32/36 or 88%.

Baseline Resting blood pressure

Despite a ~16mmHg difference in pre-training (baseline) SBP between the exercise training and control groups, baseline blood pressures were not significantly different ($P>0.05$). It was not surprising, considering the age of this cohort that many participants were taking anti-hypertensive medications, including but not limited to, ACE inhibitors, angiotensin receptor blockers, beta blockers and diuretics. On average, control group participants reported taking 3.6±1.4 anti-hypertensive medications, compared to 1.6±1.4 medications in the IET group, which may have contributed to the baseline blood pressure difference (Table 6). A weak, but significant correlation was found between pre-training resting diastolic blood pressure (DBP) and the number of anti-hypertension medications as reported by each participant (IET and control groups combined; R = -0.44; *P*<0.05). No such association between the number of anti-hypertension medications and pre-training SBP was found

12-week Resting Blood Pressure

12 weeks of handgrip IET resulted in a significant reduction in systolic blood pressure (-10.5±7.7mmHg) that was not reflected in the control group (control -4.5±6.9mmHg; *P*>0.05). Despite this, differences between groups were not significantly different. No significant changes in DBP were found in either the IET (-4.92±1.52mmHg, *P*>0.05) or the control (-2.10±3.49mmHg, *P*>0.05) groups. The group mean reductions in SBP following 12-weeks of IET were sustained through 6 and 12 weeks of detraining (121.22±2.40mmHg, at week 18; Δ ~11mmHg; and 122.19±4.02mmHg, at week 24; Δ ~11mmHg) compared to baseline.

Individual regression analyses for all participants were calculated. Individual differences in responsiveness to IET were evident with both positive and negative regression outcomes. Whole group and individual regressions for SBP were statistically significant (IET, F =44.34, -0.57± 0.08, p=<0.0001; Control, -0.21 ± 0.12, F=2.93, p=0.10), but not DBP (p>0.05). The difference between groups was significant (p=0.032).

Discussion and Conclusions

The effect of IET on RBP has been reported mostly in young, relatively healthy adults, but there is a paucity of data (<10 studies) on the efficacy of IET in elderly individuals [Millar et al. 2014] and even less data has been published from a prolonged detraining period.

12-weeks of unilateral handgrip training in elderly adults resulted in significant reductions in resting SBP, similar to previous reports [McGowan et al. 2006; McGowan et al. 2007a,b; Millar et al. 2013; Taylor et al. 2003] Moreover, not only did mean SBP reduce from ~133 to 122 mmHg during 12 weeks of training, the reduction was maintained below baseline values for up to 12 weeks after cessation of training. However, the mechanism for such a phenomenon is not known.

Establishing a relationship between length of IET and the sustainability of post-training RBP adaptations has been difficult since detraining periods have not been a feature of IET studies, except for Wiley et al. [1992]. In that case, 5 weeks of IET lead to RBP reductions that were no longer evident 5 weeks after training cessation. Moreover, most IET studies have been relatively short (3-8 weeks), except for two studies in which 10 weeks of IET was prescribed [Badrov 2013b;Taylor 2003]. However, post-IET monitoring of RBP was not included in both cases. Therefore, this is the first study to incorporate a relatively long IET program, followed by an equally long post-IET monitoring period of RBP. Using the data presented here and the data of Wiley et al. [1992], there may be a relationship between the length of training and RBP adaptation sustainability, but further investigation is required to support such an association.

In the absence of data on the sustainability of IET-induced reductions in RBP after training cessation, other forms of resistance exercise training may offer some insight. For example, 8 weeks of resistance exercise training (RT) in postmenopausal women (ages 49-62 years) reduced their resting SBP by 15 mmHg (SBP). But, this adaptation disappeared after 8-weeks of detraining [Elliott et al. 2002]. However, in another study, 12 to 14 weeks of RT in hypertensive older women and men, which lead to a marked decrease in SBP (Δ16mmHg and Δ 18 mmHg respectively) resulted in a sustained reduction in SBP after training had ended [Moraes et al. 2012; Nascimiento et al. 2014]. These data suggest a correlation between the length of the training program and the sustainability of RBP adaptations after training cessation, which aligns with the present data.

Lawrence et al. [2014] stated that the amount of IET required to maintain reduced blood pressure was not known. Blood pressure adaptations induced by IET are likely the result of multiple intersecting physiological mechanisms, where both exercise volume and duration are important components [Lawrence et al. 2014; Millar et al. 2014]. It has been suggested that short-term blood pressure adaptations and rapid return of resting blood pressure to baseline values after training cessation [Devereux et al. 2010; Howden et al. 1992; Wiley et al. 1992] may be more physiological than anatomical in nature [Millar et al, 2014]. Our detraining data, along with previous reports [Devereux et al. 2010; Howden et al. 1992; Wiley et al. 1992], suggests that the mechanisms responsible for resting blood pressure reductions induced by IHG training are phasic. During resistance exercise training, it has been suggested that nervous system changes are responsible for adaptations in the first 3-5 weeks [Kraemer et al. 1988; Kraemer et al. 1996; Moritani, 1979; Moritani and DeVries, 1980;], followed by morphological adaptations, including increased muscle fiber type cross sectional area and mitochondrial density [Gonyea & Sale 1983; MacDougall et al. 1980; MacDougall, 1986]. Shorter IET programs [e.g. Wiley et al. 1992] may not have been long enough to induce morphological adaptations, which are more likely to withstand longer detraining periods.

However, further investigations regarding the mechanisms for IET-induced reductions in resting blood pressure are warranted, to test this hypothesis.

Less than half of hypertensive adults have their blood pressure controlled and approximately 67% of adults over the age of 60 years have HTN in the US [Brook et al. 2013; Raphael et al. 2015]. In our study, reductions in SBP were equivalent to those observed in previous isometric handgrip studies in older adults [Taylor et al. 2003; McGowan et al. 2006; McGowan et al. 2007a,b; Millar et al. 2013]. Participating in physical activity and improving blood pressure management are essential for reducing cardiovascular risk [Acree et al. 2006; Fletcher et al. 2013; Gusmao et al. 2009]. For example, a 13% reduction in all-cause mortality has been suggested when resting blood pressures are reduced by 10 mmHg [Ettehad et al. 2015], which is similar to that observed following IET and evidenced by the present data.

It has been suggested that older adults may be more responsive to IET [Millar et al. 2007], but inter-individual responsiveness to IET may be a more important question than age *per se*. In the present study, IET was not universally effective and several participants did not experience a significant reduction in blood pressure. This is similar to previous studies [Ash et al. 2017; Badrov et al. 2016; Bartol et al. 2012; Stiller-Moldovan et al. 2012]. Our data supports the possibility that older participants undergoing pharmacological hypertension management are not equally-responsive to IET and that age and polypharmacy may either blunt or attenuate their responses to IET [Bartol et al. 2012; Lawrence et al. 2014; Mcgowan et al 2006; Millar et al. 2014]. A larger cohort is needed to confirm this assertion.

It has been proposed that pre-IET blood pressure is a predictor of responsiveness to training [Millar et al. 2007]. However, in the present study, baseline RBP did not predict changes in SBP in response to IET ($R(19) = -.42$; $p>0.05$) suggesting that a relationship between baseline RBP and responsiveness to IET may not be consistent throughout the lifespan. Moreover considering the heterogeneity of human participants (e.g. baseline blood pressure, age, polypharmacy and co-morbidities) a standard protocol (e.g. 4x 2mins at 30%MVC) may not be sufficient for less-responsive individuals. However, the true heterogeneity in responsiveness to IET is difficult to assess since changes in group mean blood pressure are most often reported. Therefore, we propose development of guidelines for testing and prescribing IET as a critical step in improving successful IET-induced RBP reductions in larger populations. However, in order to determine potential guidelines the challenge would be in identifying the most important modifiable IET elements (e.g. muscle exercised, intensity, and time) for program design and exercise prescription.

This study was limited in several ways. First, the control group comprised only 5 participants compared to 19 in the IET group. An unbalanced sample size may not accurately represent the true effects of IET. The primary challenge was that many prospective participants were unwilling to be randomized into the control. They made IET group allocation a condition of their participation in the study. However, this may be important with respect to the success of IET when prescribed as a “face-to-face” program (see chapter 4 for a detailed discussion). Previous reports suggest that older adults (>60 years) prefer exercising in aged-matched groups compared to exercising alone [Beauchamp et al. 2007].

Results of this study provide evidence to support the benefits of group IET on SBP in an elderly population. The authors acknowledge that unilateral, and alternating unilateral IHG, bilateral leg extension, and isometric wall squat are among the isometric exercise modes reported. Factors like safety, convenience, and cost effectiveness should be considered when optimizing IET protocols. Elderly adults often present with musculoskeletal disorders such as osteoarthritis and skeletal muscle weakness, leading to functional limitations [McAlindon et al. 1993; Slemenda et al. 1997]. However, the participants in this study were easily capable of performing 2 minute isometric handgrip exercise at 30% MVC without undue discomfort. In fact, this type of training also improved grip strength, independent of hand dominance, by 10% and 15%, (left and right hand respectively). This is an additional useful adaptation in this age group for improved capacity to complete activities of daily living.

Conclusions

The findings of this study provide valuable support that 12-weeks of isometric handgrip exercise can lead to significant reductions in resting blood pressure, that are sustained for 12-weeks after training cessation. We have demonstrated for the first time the persistence of the effects of an extended IET program in older adults with various comorbidities. Given that responses to current IET programs, using well accepted protocols have been varied it is possible that developing individualized training programs is a necessary next step to broadening the scope of IET for the greater hypertensive community. At this time nothing is known about how much IET is required to maintain resting blood pressure adaptations after a significant reduction in RBP is achieved. Perhaps when completing >12 weeks of IET, a maintenance program, comprising single sessions per week or tapering sessions over several weeks, may be sufficient to maintain the benefits that have been achieved, in the longer-term.

Tables

Table 5: Participant Demographics

Group	N	Male (N)	Female (N)	Age (mean)	BMI (mean)	HTN	Diabetes	COPD
Control	5	3	2	73 ± 3.8	31.0 ± 2.1	N = 5	N = 1	N = 0
IHG	19	5	14	73.37 ± 1.5	28.9 ± 1.3	N = 15	N = 4	N = 4

Values are means ± SEM: IHG: isometric handgrip exercise; BMI: body mass index; HTN: hypertension; COPD: chronic obstructive pulmonary disease.

Table 6: Participant antihypertensive medications by class.

Group	**SEX**	**Antihypertensive Medications**	
Control	Female = 2	ACE-I	N= 2
	Male = 3	ARB	N= 2
		BB	N= 4
		BT	N= 2
		CCB	N= 2
		Vaso	N= 0
		ANG II B	N= 0
		DIU	N= 2
		None	N= 0
IHG	Female = 14	ACE-I	N= 0
	Male = 5	ARB	N= 7
		BB	N= 5
		BT	N= 2
		CCB	N= 4
		Vaso	N= 0
		ANG II B	N= 0
		DIU	N= 8
		None	N= 7

Values are means ± SEM. IHG: isometric handgrip exercise; BMI: body mass index; HTN: hypertension; COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; CHF: congestive heart failure; T2D: type II diabetes; Renal: renal disease or kidney disease; CABG: coronary artery bypass graft; ACE-I: ace inhibitor; ARB: angiotensin receptor blocker; BB: beta blocker; BT: blood thinner; CCB: calcium channel blocker; Vaso: vasodilator; ANG II: angiotensin II blocker; DIU: diuretic.

Figures

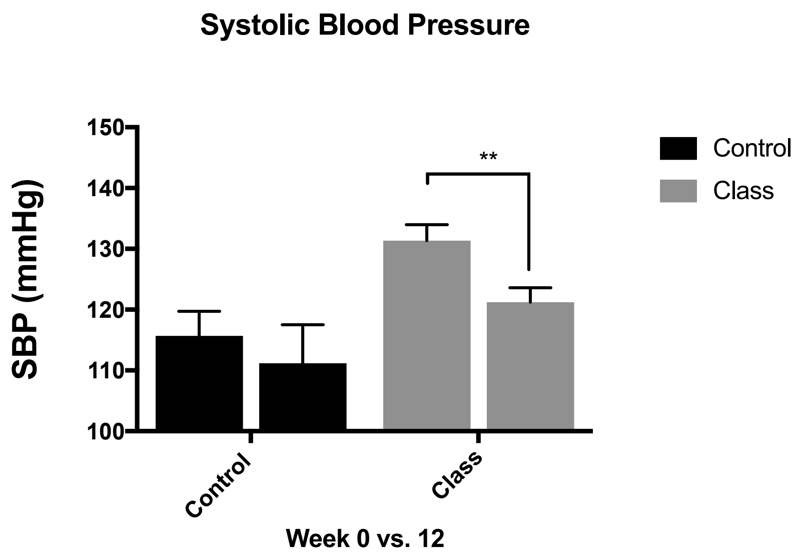


Figure 9: 12-weeks of IHG resulted in a significant reduction in group mean systolic blood pressure (SBP). Differences observed week 0 vs. 12 (p=0.007). No significant differences observed in control participants. Control week 0 vs. week 12, p=0.11

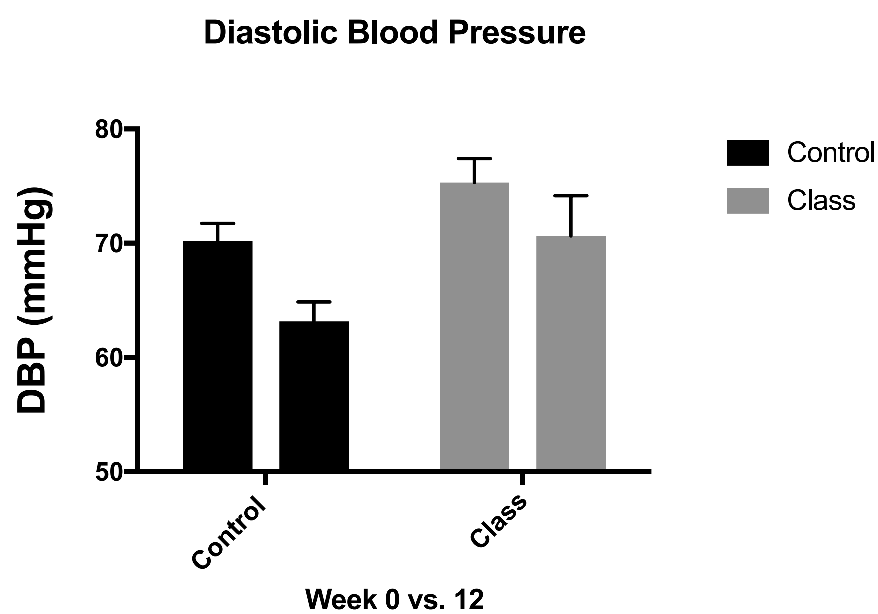


Figure 10: No significant differences observed from week 0 -12 in either the Control or IHG groups. p=0.56 and p=0.38 respectively.

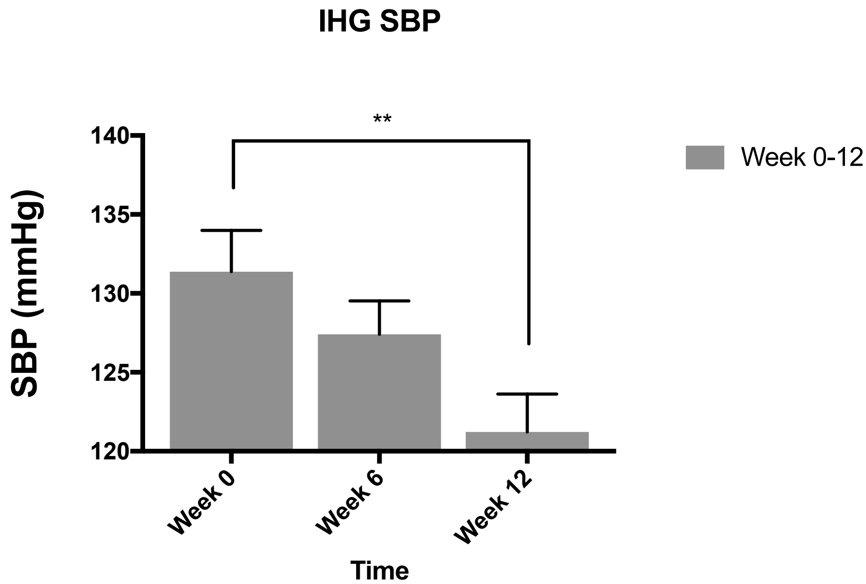


Figure 11: 12-weeks of IHG resulted in a significant reduction in group mean systolic blood pressure (SBP). Differences observed week 0 vs. 12. p= 0.007 [wk 0: 131 mmHg; wk 12: 121.2 mmHg]

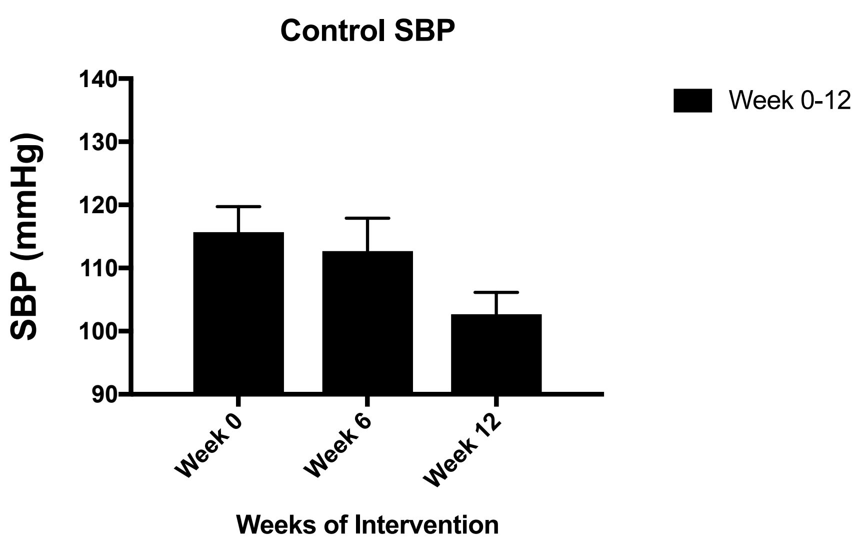


Figure 12: Group mean systolic blood pressure (SBP). No significant difference observed from week 0-12; p=0.09

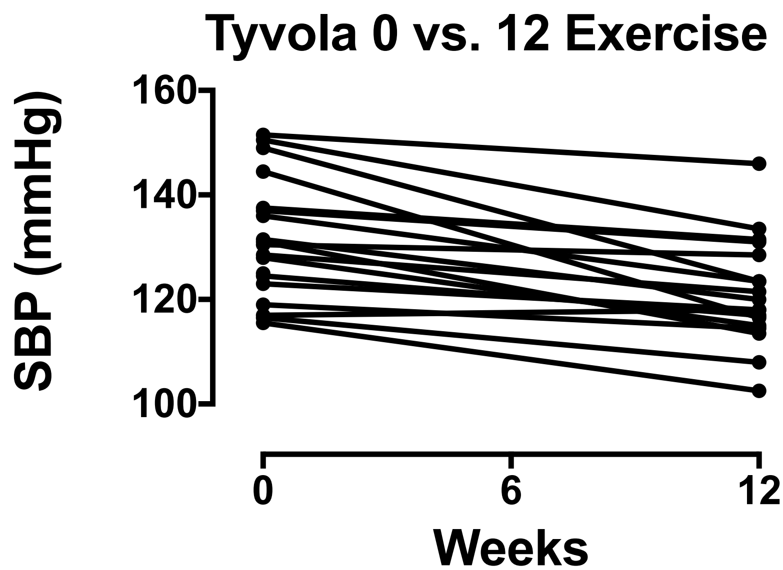


Figure 13: Individual IHG participant change in systolic blood pressure between baseline (week 0) and week 12. p<0.05.

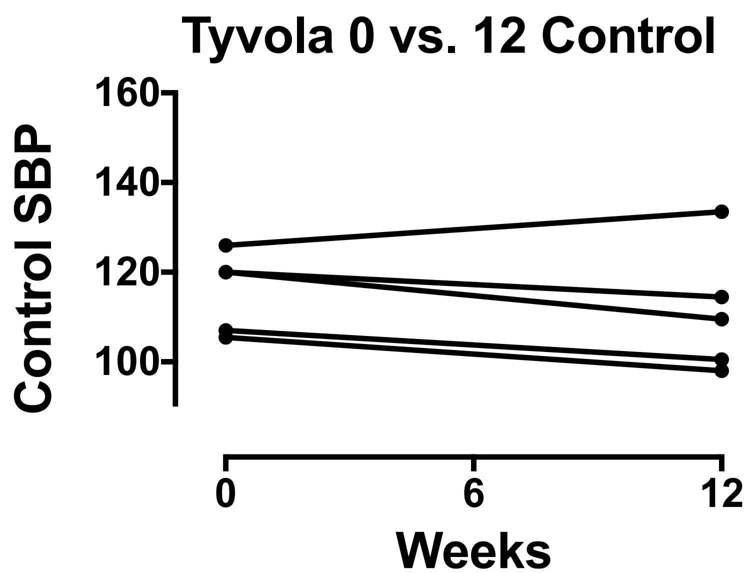


Figure 14: Individual Control participant change in systolic blood pressure between baseline (week 0) and week 12. p<0.05.

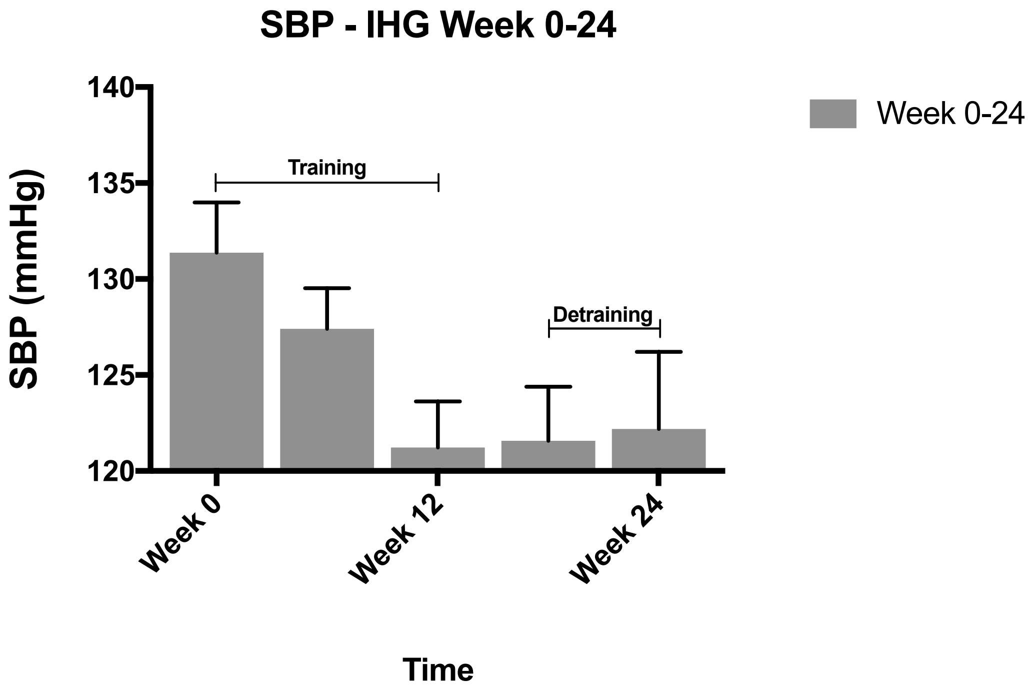


Figure 15. Resting blood pressure IHG exercise group, week 0 – 24 weeks
12 weeks of IHG training resulted in a reduction in SBP (training -10.5±7.7mmHg, control -4.5±6.9mmHg; p=0.03). Post exercise training at 18 weeks and 24 weeks reductions in SBP were still significantly below baseline but not significantly higher or lower compared to 12-weeks

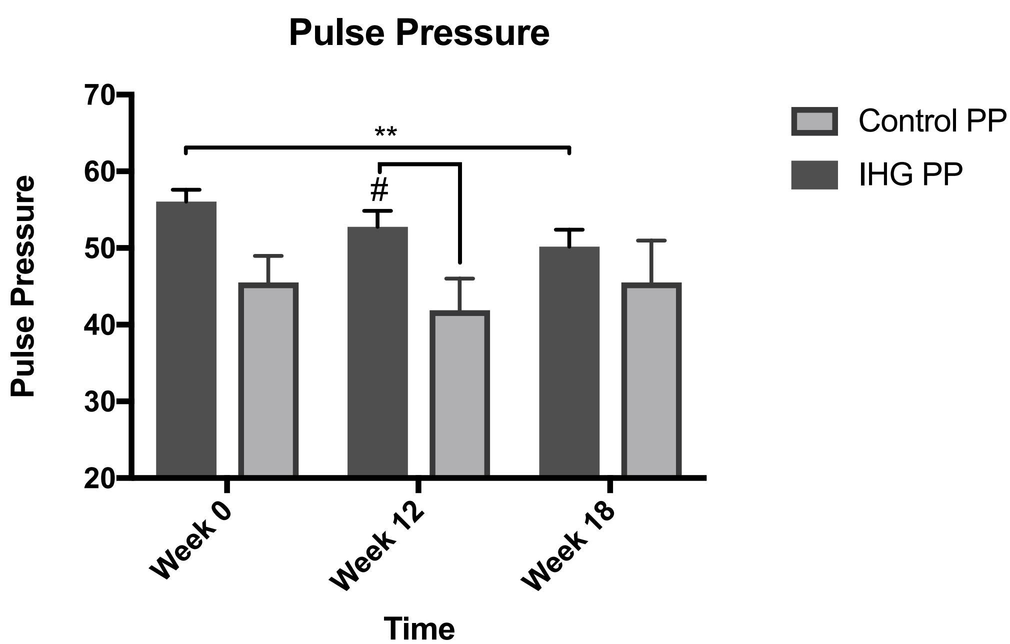


Figure 16. The effects of IET on pulse pressure in control and IHG. Significant difference (i.e. reduction in PP) from week 0-18 (p=0.004) in IHG. PP was significantly different at week 12 between groups (p=0.05)

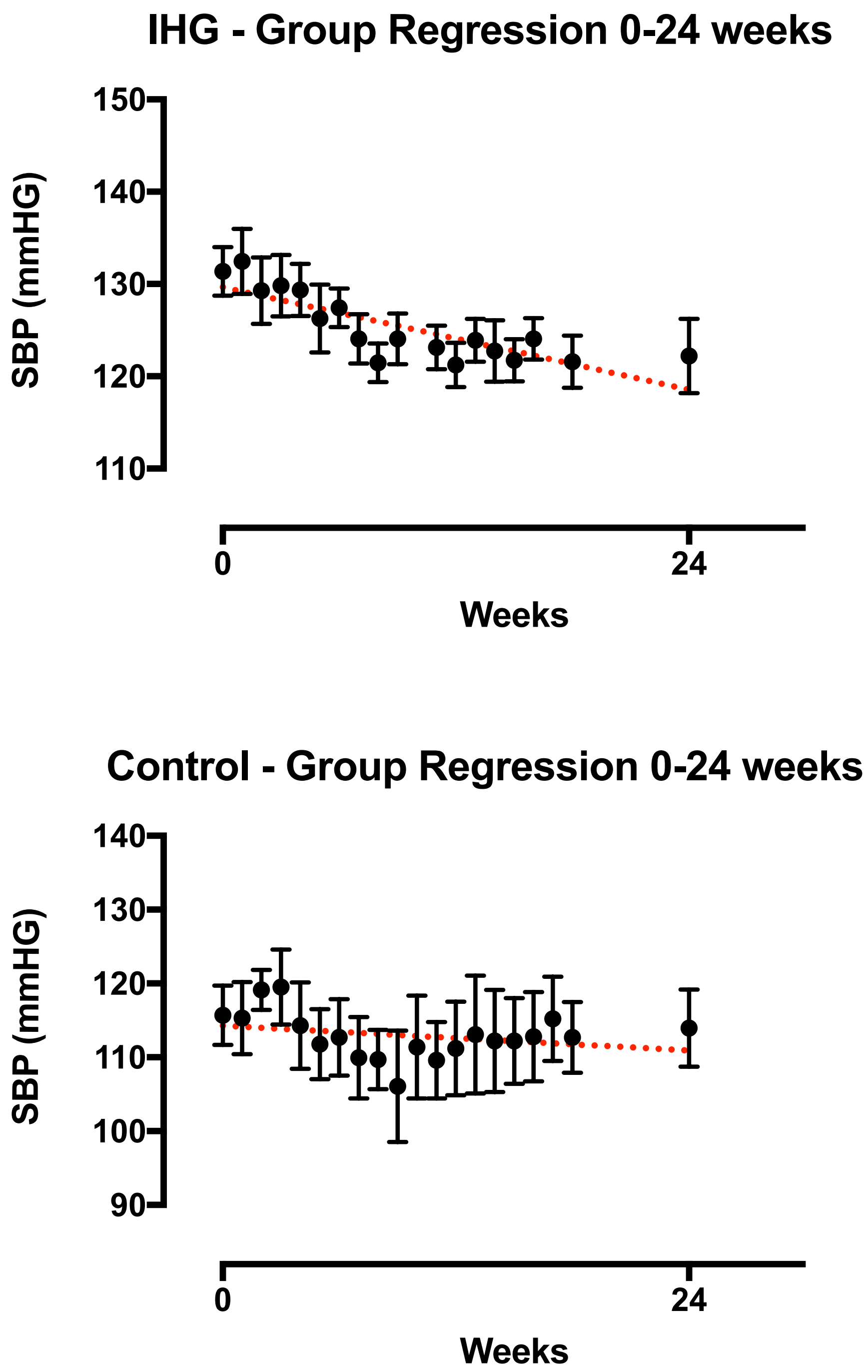


Figure 17a, b: Group regression analyses for change in SBP from baseline (week 0) to detraining week 24. IHG P<0.0001 Deviation from zero, significant. Control P=0.2228 Deviation from zero, not significant.

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CHAPTER 3: "GET A GRIP ON HYPERTENSION": EXPLORING THE USE OF ISOMETRIC HANDGRIP TRAINING IN CARDIOPULMONARY REHABILITATION PATIENTS

The work in this chapter was presented at the American College of Sports Medicine Southeast Region Annual Meeting (2016)

Abstract

Purpose: Isometric handgrip training (IHG) lowers systolic and diastolic blood pressure (SBP/DBP), but the efficacy of IHG training in aiding recovery in the cardiac/pulmonary disease rehabilitation setting has not yet been investigated. Methods: Participants (n=11; 50-80 years old) from a local cardiac/pulmonary rehabilitation program were randomized to IHG (n=6) or control (no treatment; n=5) groups. IHG participants completed an IHG training program which involved 30% maximal voluntary contraction (MVC), 3 days a week for 6-weeks. Resting SBP, DBP, and heart rate (HR) were assessed weekly in both groups. Results: Reductions in SBP were observed in 3 of the 6 IHG participants (group mean -16 ± 11 mmHg; p = 0.12) and DBP was reduced in 2 of 6 participants (group mean -9 ± 1 mmHg; p = 0.06) compared to baseline. Among the control group, SBP was reduced in 2 of 5 participants (group mean -11 ± 7 mmHg; p = 0.26) and DBP was significantly reduced in 4 of the 5 participants (group mean -7 ± 4 mmHg; p = 0.04). No significant group interaction between treatment and time was found for SBP (p=0.31) or DBP (p=0.22). Conclusions: Group mean data for SBP and DBP following IHG training have most often been reported. However, reporting individual blood pressure changes may be more informative. Our data suggest that standard IHG training may be inadequate for patients immediately following a major cardiac/pulmonary event. Future work with a larger cohort to determine the true effect of IHG training in cardiopulmonary disease patients is warranted.

Introduction

Evidence supporting the efficacy of exercise-based cardiopulmonary rehabilitation is associated with reduced all-cause mortality and improves systolic BP (SBP) compared to controls, but results are inconsistent [Jolliffe et al. 2001].

Outpatient cardiopulmonary rehabilitation patients often face difficulty with traditional modes of exercise and are at risk for uncontrolled elevations in BP, particularly in response to resistance training [Vanhees et al. 2012]. Isometric handgrip (IHG) training is an exercise intervention that requires minimal exertion and does not substantially increase BP during the activity [Araujo et al. 2011; Goessler et al. 2016; Olher et al. 2013]. These patients may benefit significantly from IHG as clinically relevant reductions in SBP and diastolic BP (DBP) (>2mmHg) could help reduce the burden of HTN [Chobanian et al. 2003] and reduce dependency on anti-hypertensive medications. However, the efficacy of IET in cardiopulmonary disease patients has not been sufficiently investigated. Therefore, the primary aim of this study was to investigate the effect of a 6-week IHG training program on RBP in a cohort of active cardiopulmonary rehabilitation patients.

Methods

Participants

This study was approved by the institutional review board (IRB) of the Carolinas Healthcare System. Participants were recruited from an outpatient phase II/III cardiopulmonary rehabilitation facility and volunteered to participate (Table 7). All participants had a history of existing cardiopulmonary disease [coronary artery disease (CAD), heart failure, recent myocardial infarction, angioplasty, coronary artery bypass graft (CABG) or chronic obstructive pulmonary disease] and were cleared for exercise by their primary care physician or cardiologist.

Participants were provided written explanation of all requirements and procedures, and gave informed consent to participate. The diverse group of participants were randomized to IHG exercise (6 males and 0 females; 68.5 ± 2.80 years; 32.9 ± 2.34 kg/m^2) or control (4 males and 1 female; 72.6 ±3.69 years; 26.76 ± 1.02 kg/m^2) groups. All participants were actively attending their rehabilitation program 2-3 days per week and continued throughout the study, were non-smokers, and were asked to continue use of current prescription medications for the duration of the study (Table 8). All participants agreed to abstain from food for 2 hours, caffeine or alcohol for 12 hours, and vigorous exercise for 24 hours before resting BP assessment. All participants completed weekly screening questionnaires confirming their adherence to the procedures as described and to ensure no significant changes had been made in diet, medications, or lifestyle.

Within the study population, 90% had been diagnosed with CAD, 54% of participants had undergone CABG procedures, 45% had type II diabetes, 45% had at least one stent placed, 36% had pulmonary related complications and 18% of patients had heart failure. Furthermore, all participants were diagnosed with HTN and prescribed anti-hypertensive medications. Moreover, these participants were taking on average three (IHG group) and two (control group) anti-hypertensive medications during the study. Most frequently prescribed medications included calcium channel blockers (72%), angiotensin II blockers (54%), diuretics (45%), and beta-blockers (36%).

Study Protocol

Before data collection, all participants were required to attend an orientation session for familiarization with study procedures. Following established procedures, [Pickering et al. 2003] RBP and heart rate (HR) were measured in duplicate once per week during the study (Adview® 9000 American Diagnostic Corporation, Hauppauge, NY). If RBP measures differed by 20% (SBP or DBP) a third measure was taken, and the three measurements were averaged. All RBP and HR measures were made within 1-2 hours of the initial baseline measure to account for circadian variation. Final measures were collected between 24 and 72 hours following a participant's last IHG training session.

Isometric Handgrip Training

IHG exercise was performed 3 days per week for 6-weeks with the dominant hand, using an electronic handgrip dynamometer assigned to each participant (Camry, 200lb Handgrip Dynamometer, City Industry, CA). IHG sessions comprised 2-minute IHG contractions at 30% of MVC with 1 minute of rest between each contraction (x4). Maximum voluntary contraction (MVC) was established on each IHG training day by completing 3 handgrip MVCs, with the highest of the three selected as the intensity (kg) for that day as previously described in chapter 1. Instructor feedback and encouragement was provided during each session to ensure compliance. Members of the control group participated in all procedures except IHG training.

Statistical analysis

All data were analyzed using SAS statistical software (SAS Institute Inc., Cary, NC) and GraphPad Prism Software (GraphPad Software Inc., La Jolla, CA). Basic statistics were reported as means and standard error of the mean (SEM). To test differences between groups, we first calculated individual regression coefficients using a general linear model (GLM) and included weighted and non-weighted analyses to control for attendance. Mean regression coefficients for resting blood pressure were then calculated and analyzed for each group and tested for differences using a Student *t-test*. An analysis of covariance (ANCOVA) was used to analyze both whole group and individual RBP over the course of IHG (weeks 0-6). Because considerable heterogeneity in resting BP was identified between groups at week 0; a secondary analysis was completed after removing week 0 to test for significance from week 1-6. We tested for a treatment x time interaction, and the alpha level was set at $p < 0.05$.

Results

In this study, adherence to the intervention was not 100% in this particular patient cohort, unlike adherence reported by others, studying participants with less severe disease [Badrov et al. 2013a, b; Badrov et al. 2016; Bartol et al. 2012]. This cohort of cardiopulmonary rehabilitation patients completed approximately 78% (14/18) of IHG exercise sessions and therefore still more than ¾ of the planned training sessions. Both whole-group and single-participant regression analyses were not significant for either SBP (p=0.12) or DBP (p=0.58) in both the IHG (SBP-1.04±2.00; DBP-0.32±1.06 mmHg) and control (SBP 0.43±1.87; DBP -0.44± 0.81 mmHg) participants. Six weeks of IHG training did not result in statistically significant reductions in either SBP or DBP between the control and exercise groups (p=0.31; p=0.22) compared to baseline. Further review of our data showed significant heterogeneity in participant BP between week 0 (baseline) and week 1. Therefore, a secondary analysis was completed after dropping week 0 from the model. A statistically significant negative regression result ($p = 0.02$; slope = -1.12) for SBP was achieved between groups using weeks 1-6 only.

Despite a lack of statistical significance from the primary analysis in our results, individual clinically-relevant reductions (e.g. >2mmHg) in SBP from baseline to week 6 were observed in 3 of the 6 participants (-16 ± 11 mmHg; $p = 0.12$, Figure 23) and DBP was reduced in 2 of the 6 IHG participants (-9 ± 1 mmHg, $p = 0.06$). DBP was reduced in 4 participants (-7 ± 4 mmHg, $p = 0.04$) and SBP was reduced in 2 of the 5 control participants (-11 ± 7 mmHg, $p = 0.26$, Figure 23). Whilst we aimed to control for factors that may influence RBP, two participants in the control group and one participant in the IHG group did undergo a medication change at weeks one and two. In these participants, reductions in SBP and DBP were observed at the end of the intervention period.

Discussion and Conclusions

To our knowledge, only two studies have investigated the effects of IHG in a clinical setting (e.g., diagnosed coronary artery disease). Both of these studies included only a single session handgrip exercise. [Araujo et al. 2011; Goessler et al. 2016]. Hence, the present study is the first to assess adaptations in RBP with active cardiopulmonary rehabilitation patients, using isometric handgrip training for 6 weeks. Importantly, we demonstrated that performing IHG with handgrip dynamometers during a 6-week intervention was well tolerated by cardiopulmonary rehabilitation patients. While RBP was lower in several participants after training, similar to those observed in meta-analyses and other isometric exercise investigations [Badrov et al. 2013; Badrov et al. 2016; Baross et al. 2012; Owen et al. 2010] group mean responses were not significantly different, compared to baseline or between groups. As outlined above, reductions in SBP were statistically significant after excluding week 0 data. We performed this secondary analysis due to variation in RBP measures in week 0. This highlights the need for longer pre-study measurement periods in this type of patient population, to allow for familiarization with the IHG training and study procedures.

Despite growing evidence to support IHG-induced reductions in RBP, not all participants are equally responsive to the established isometric training protocol [Badrov et al. 2016; Bartol et al. 2012; Stiller-Moldovan et al. 2012]. Several studies have shown differential responsiveness in individual participants (e.g., medicated hypertensive patients) including reductions, elevations, or no change in RBP after acute and chronic isometric interventions [Badrov et al. 2016; Bartol et al. 2012; Goessler et al. 2016; Olher et al. 2013; Pagonas et al. 2017; Stiller-Moldovan et al. 2012]. In the present study, the range of RBP changes in the IHG group was -28 to +18 mmHg SBP and -10 to +11 mmHg for DBP, relative to baseline. Moreover, the variation in control group responses (-16 to +13 mmHg systolic and -12 to +3 mmHg diastolic) was not anticipated, despite careful use of established procedures for recording RBP. Importantly, participants were enrolled in a rehabilitation program while suffering from significant cardiopulmonary illness, or recovering from surgical intervention. Therefore, their therapeutic interventions, which included physical activity and pharmacological intervention may have been a confounding factor. These activities may have influenced RBP during the IHG training period and future study designs should take note of this important issue.

The IHG protocol (30% MVC, 2-min contractions with 1 minute rest periods, x4) used in this study has induced RBP reductions in normotensive and non-medicated hypertensive participants across a large range of ages [Badrov et al. 2013a,b; Badrov et al. 2016; Millar et al. 2008; Millar et al. 2013]. Previous studies have excluded participants presenting with multiple co-morbidities and significant cardiopulmonary complications [Badrov et al. 2013a,b; Badrov et al. 2016; Bartol et al. 2012; Millar et al. 2008; Millar et al. 2013; Olher et al. 2013] However, the multiple comorbidities and poorer general health status observed among our patient population (e.g., heart disease, diabetes, COPD, >2 HTN medications) may have been important factors in the differential responsiveness to IHG training [Goessler et al. 2016; Olher et al. 2012; Stiller-Moldovan et al. 2012]. Moreover, 3 participants (2 control and 1 IHG) had their anti-hypertensive medications modified during week 1 and 2 of the study. This, unanticipated modification to patient medication may have influenced IHG training responsiveness [Goessler et al. 2016; Stiller-Moldovan et al. 2012] and must be accounted for in future research with this population.

The pharmacotherapy load and the combination of drug classes that were prescribed may either attenuate or blunt responses to IHG training. , A larger cohort would establish whether such an association exists. Overall, this variability in responsiveness suggests individualized IHG training programs may be required to elicit effective BP adaptations in patients with a lower health status and specific pharmacotherapy. However, the challenge would then be in identifying individual patient need for specific isometric exercise prescriptions [Vanhees et al. 2012].

Downward trends in RBP following IHG were greatest at weeks 4-5. However, at 6-weeks, the group mean RBP was higher than or equal to baseline values.. Whilst our results were not significant, increased group and individual RBP at week 6 is inconsistent with previous IHG reports [Badrov et al. 2013a,b; Badrov et al. 2016; Millar et al. 2008;

Baross et al. 2012]. It is possible that participants may have interpreted their final session as a “test” and a white coat effect may have been responsible for the increased RBP values during the final session [Howden et al. 2002].

Despite being underpowered, our study provides important guidance for future IHG training research in this particular clinical population. Future studies should recruit a large multicenter cohort of cardiopulmonary disease patients to effectively assess the efficacy of IHG, perhaps using a range of isometric exercise protocols to determine maximum effectiveness. Additionally, outcomes should be stratified based on patient clinical or demographic characteristics such as medication use and disease status (i.e., recent cardiovascular event, adequate management). Longer pre-measure baseline measures should be completed to account for a potential placebo effect on blood pressure. Finally, understanding the characteristics of responders and non-responders to IHG training may help to design individualized training protocols to enhance the likelihood of success in participants with poor health conditions and overt cardiopulmonary disease.

Tables

Table 7: Participant Demographics

Group	N	Male (N)	Female (N)	Age (mean)	BMI (mean)	HTN	Diabetes	COPD
Control	5	4	1	72.6 ± 3.6	26.7.0 ± 1.0	N = 5	N = 1	N = 2
IHG	6	6	0	68.5 ± 2.8	32.9 ± 2.3	N = 5	N = 3	N = 1

Values are means ± SEM : IHG: isometric handgrip exercise; BMI: body mass index; HTN: hypertension; COPD: chronic obstructive pulmonary disease.

Table 8: Participant medications and disease and comorbidities.

Group	SEX	Antihypertensive Medications		Diseases and Comorbidities	
Control	Female = 1	ACE-I	N= 1	HTN	n= 5
	Male = 4	ARB	N= 2	CVD	n= 6
		BB	N= 0	CHF	n= 1
		BT	N= 4	COPD	n= 2
		CCB	N= 4	T2D	n= 3
		Vaso	N= 2	RENAL	n= 1
		ANG II B	N= 2	STROKE	n= 0
		DIU	N= 1	STENT	n= 3
		None	N= 0	CABG	n= 3
IHG	Female = 0	ACE-I	N= 1	HTN	n= 5
	Male = 6	ARB	N= 2	CVD	n= 5
		BB	N= 4	CHF	n= 1
		BT	N= 6	COPD	n= 2
		CCB	N= 4	T2D	n= 1
		Vaso	N= 0	RENAL	n= 0
		ANG II B	N= 4	STROKE	n= 1
		DIU	N= 4	STENT	n= 2
		None	N= 0	CABG	n= 3

Values are means ± SEM : IHG: isometric handgrip exercise; BMI: body mass index; HTN: hypertension; COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; CHF: congestive heart failure; T2D: type II diabetes; Renal: renal disease or kidney disease; CABG: coronary artery bypass graft; ACE-I: ace inhibitor; ARB: angiotensin receptor blocker; BB: beta blocker; BT: blood thinner; CCB: calcium channel blocker; Vaso: vasodilator; ANG II: angiotensin II blocker; DIU: diuretic.

Figures:

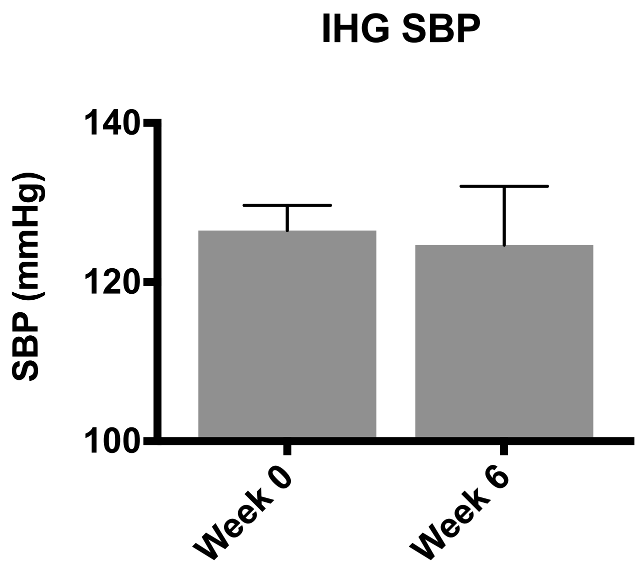

Figure 18: Group mean systolic blood pressure (SBP). No significant difference observed from week 0-6 p>0.05

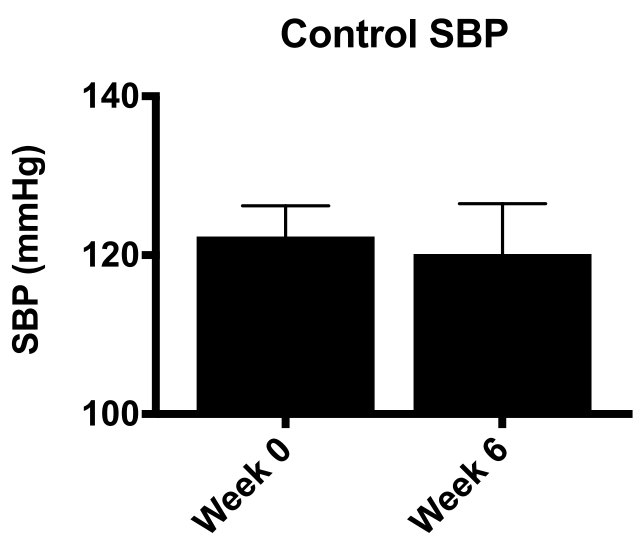

Figure 19: Group mean systolic blood pressure (SBP). No significant difference observed from week 0-6; p>0.05

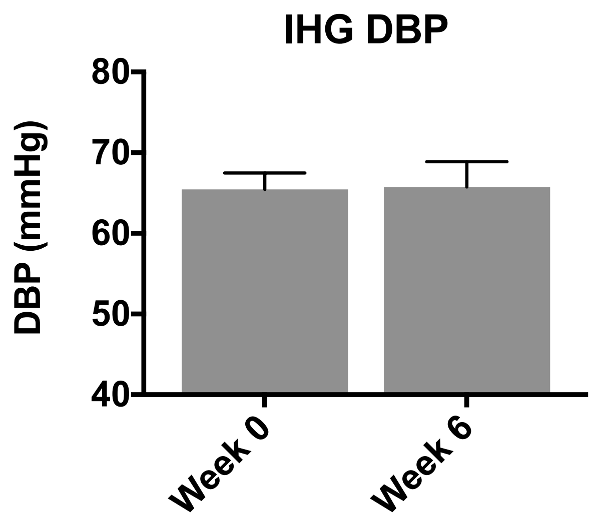

Figure 20: Group mean diastolic blood pressure (DBP). No significant difference observed from week 0-6; p>0.05.

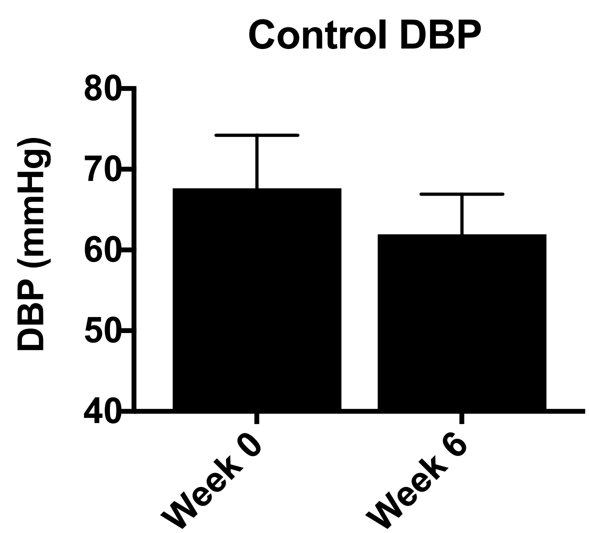

Figure 21: Group mean diastolic blood pressure (DBP). No significant difference observed from week 0-6; p>0.05.

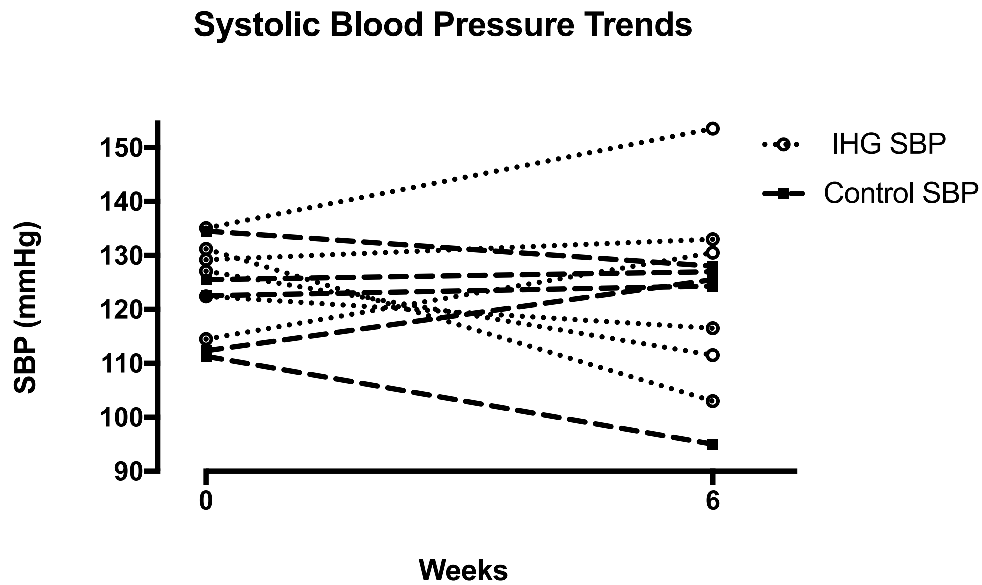

Figure 22: Individual isometric handgrip (IHG) change in systolic blood pressure (SBP) between baseline and week 0.

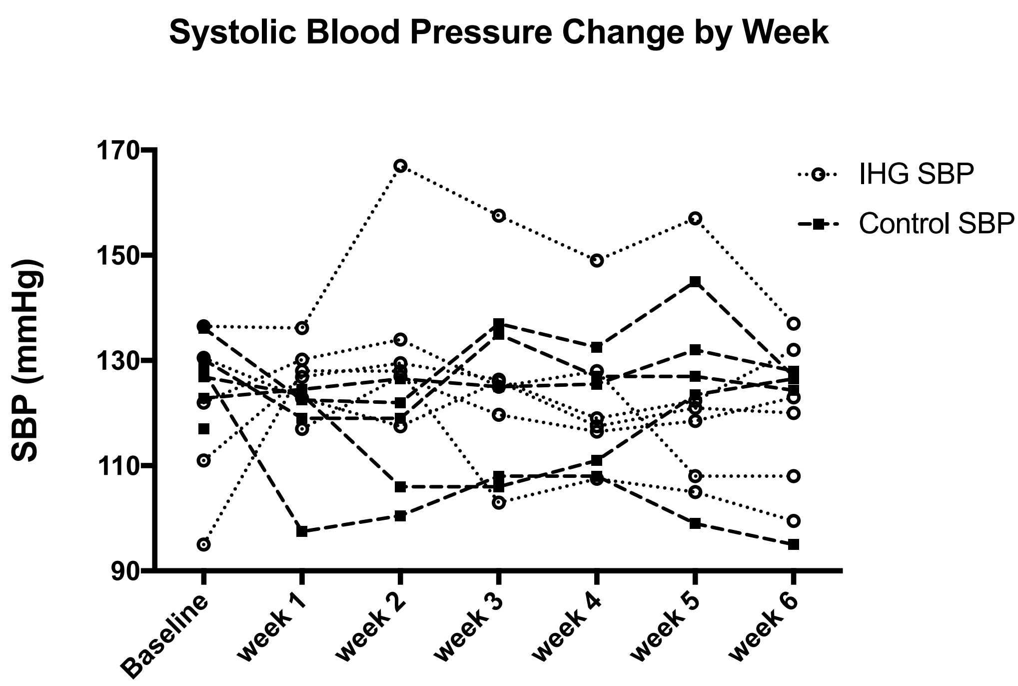

Figure 23: Individual participant change in systolic blood pressure (SBP) between baseline and week 0 in IHG and Control participants.

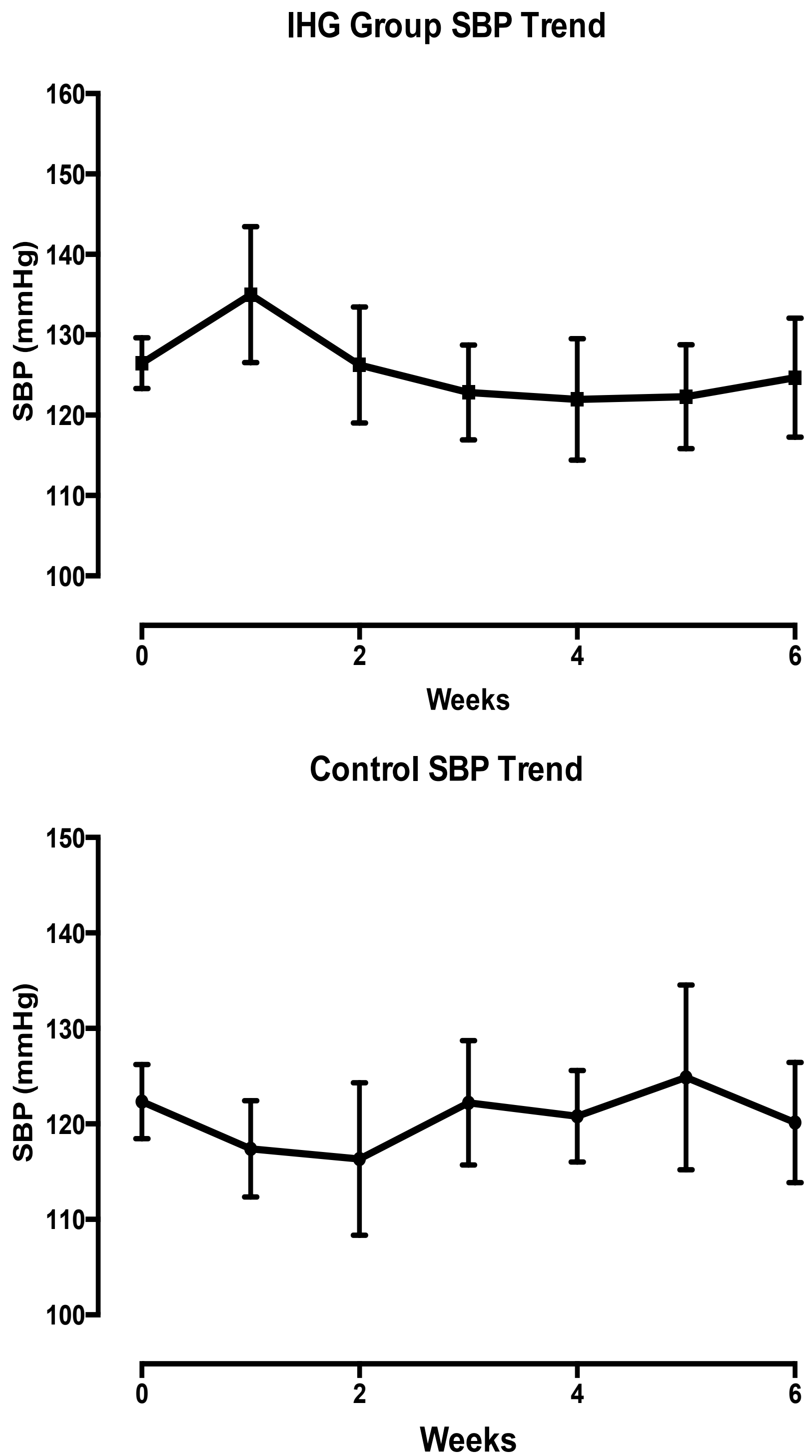

Figure 24 a,b: Mean changes in SBP in the control and exercise groups were 0.44 ± 1.88mmHg (SD) and -1.11 ± 2.37mmHg (SD). Mean changes in DBP in the control and exercise groups were 0.45 ± .82mmHg (SD) and -0.32 ± 1.16mmHg (SD). Treatment and time interactions were non-significant (p=0.31; p=0.22).

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CHAPTER 4: A COMPARISON OF BLOOD PRESSURE REDUCTIONS FOLLOWING 12-WEEKS OF ISOMETRIC TRAINING IN THE LABORATORY OR AT HOME

The work in this chapter was presented at the American College of Sports Medicine National Annual Meeting (2017) and has been published as an abstract.

Abstract

Purpose: Isometric exercise training (IET) induced reductions in resting blood pressure (RBP) have been achieved in laboratory environments, but data in support of IET outside the lab is scarce. The aim of this study was to compare 12-weeks of home-based (HOM) IET with laboratory-based, face-to-face (LAB) IET in hypertensive adults. Methods: 25 hypertensive participants (24-60 years) were randomized to three conditions; HOM, LAB or control (CON). IET involved isometric handgrip training (4 x 2-minutes at 30% maximum voluntary contraction, 3 days per week; 30%MVC). RBP was measured every 6-weeks (0, 6 and 12 weeks) during training and 6-weeks post-training (18 weeks). Results: 12 weeks of IET induced a significant reduction in mean RBP (9.1 ± 4.1 mmHg; $p < 0.10$), which was sustained for 6 weeks following cessation of training (8.3 ± 4.4 mmHg; $p < 0.10$) in the LAB group. RBP was significantly reduced in the HOM group after 12 weeks of training (9.7 ± 3.4 mmHg; $p < 0.10$) but returned to baseline after training ceased. Reductions in SBP achieved with training were observed for an additional 6 weeks after training had ended; in LAB (7.7 ± 4.5 mmHg) and HOM (5.5 ± 3.4 mmHg) groups. Clinically relevant reductions in DBP were observed following IET, but results were not significant ($p > 0.10$). Conclusions: Unsupervised home-based IET programs present an exciting opportunity for community-based strategies to combat

hypertension. However, more work is needed to understand the influence of other factors that affect RBP adaptations to IET if it is to be employed routinely outside the laboratory.

Introduction

Many IET investigations incorporate both handgrip and double-leg exercise protocols, with participants and investigators meeting face-to-face for periods of three to ten weeks [Badrov et al. 2013a; Devereux et al. 2010; Gill et al. 2015; Howden et al. 2002; Millar et al. 2013; Stiller-Moldovan 2012; Wiles et al. 2010; see chapters 2, 3 & 5].

Albeit effective, time and travel requirements for participants as well as time spent by researchers have been significant, which is impractical for implementing IET at the population level, especially for extended periods of time. It has been suggested that even when a short duration exercise program like IET is administered, travel requirements, access to specialized equipment, and associated costs may outweigh the perceived potential benefits (e.g. RBP reduction) of the intervention [Belza et al. 2004; Gillen and Gibala 2013; Lascar et al. 2014; Sallis and Hovell, 1990; Sallis et al. 1992; Trost et al. 2002].

Several investigations have used programmable and fully-automated handgrip dynamometers with integrated tracking and guiding software that can cost in excess of $500.00 USD per unit [Goessler et al. 2018; Millar 2011; Millar et al. 2009;] and may not be covered by the participant's insurance provider. Others have reported reductions in RBP using cheaper spring loaded devices [Millar et al. 2008; Mostoufi-Moab et al. 1998]. Our research group uses a cost effective simple handgrip dynamometer that provides real time measurable and quantifiable feedback at an approximate cost of ~$25.00-$30.00 USD per unit, eliciting similarly observed reductions in RBP compared to other IHG investigations [Badrov et al. 2013a,b; Badrov et al. 2016; Goessler et al. 2018; McGowan et al. 2006; McGowan et al. 2007a,b; Millar et al. 2008; Millar et al. 2013; Taylor et al. 2003; Wiley et al. 1992; See chapters 2 & 3].

The health benefits of lowering RBP are substantial and research has shown these positive effects are likely to be the result of compliance with regular exercise participation [Cornelissen 2009; Farinatti et al. 2005; Farinatti et al 2016; Hua et al., 2009; Johnson et al. 2014; Staffileno et al 2007]. Therefore, recent emphasis has been placed upon integrating successful exercise interventions into a home-based setting to combat the barriers associated with supervised exercise programs [Anderson et al. 2017; Clark et al. 2010; Dalal et al 2010; Fakhry et al. 2011 King et al., 1991]. Data on the RBP- lowering effects of home-based aerobic and resistance programs in populations of hypertensive individuals are limited [Clark et al. 2010; Farinatti et al. 2005; Farinatti et al 2015; Hua et al; 2009; Staffileno et al. 2007]. Moreover, only two home-based IET studies have been published [Goessler et al. 2018; Wiles et al. 2017], one of which used handgrip exercise [Goessler et al. 2018].

Despite recent findings supporting the benefits of IET, the efficacy of home-based , unsupervised IET programs is largely unknown. There has not been any previous direct comparisons. To the best of our knowledge, no direct comparison between home-based (i.e. conducted outside a supervised laboratory environment) IET and laboratory-based IET (i.e. supervised training in the lab) has been completed. Therefore, such a comparison (of a home-based versus lab-based IET) is necessary to better understand the potential for this simple intervention to be implemented at the population level. Furthermore, published evidence supports the use of web-based materials to support exercise interventions for the treatment and management of chronic disease, to reach a wider audience and further combat barriers associated with exercise [Kuijpers et al. 2013]. However, no previous studies have explored the translation of an isometric exercise intervention into a user-friendly, time and cost-effective format, using a web-based video platform. This format could provide useful additional support for IET as a convenient method for combatting HTN. Therefore, the purpose of this study was to determine whether home-based IET elicits significant and sustained reductions in RBP, in adults with hypertension compared to a well-established laboratory-based IET protocol.

Methods

Participants

The University of North Carolina at Charlotte institutional review board approved all protocols and procedures of this investigation prior to study enrollment. 21 hypertensive or pre-hypertensive participants (Age 49.71 ± 2.26 and BMI 31.25 ± 1.31 kg/m^2) were recruited to participate (Table 9). Inclusion criteria for participation in the study were: faculty/staff member or graduate student status, between the ages of 21 and 60yrs, RBP measured between 130/81 and 160/100mmHg and/or those individuals currently prescribed medication to manage hypertension, for a period of at least 6-months at the time of enrollment. Participants possessed no contraindications to performing maximal isometric handgrip (IHG) contractions, and were able to understand the informed consent and other procedures relating to the performing of IET. Individuals presenting with physical limitations to completing IET or uncontrolled high blood pressure, outside of these inclusion parameters were excluded from the study.

Participants who met these criteria were invited to the research laboratory and attended an orientation session where they provided written informed consent and completed baseline assessments (see chapter 1, General Methods). Following informed consent, participants were randomized to one of three study groups; laboratory-based (LAB) IET, home- based (HOM) IET (with instructional web-based video), and a control (CON) condition.

IET instructional videos

Two members of the research team, a Certified Clinical Exercise Physiologist with experience administering IET protocols and the other a Certified Health Education Specialist with public health intervention expertise created the instructional isometric exercise training videos. Video extras included a group of diverse graduate students from the University's Department of Kinesiology, all with experience at completing IET procedures. Instructional videos were filmed in the University's Home Simulation lab, in order to mimic a similar environment to that in which participants were to engage in the training program. Still images captured from the videos may be found in Figures 6a and 6b in the General Methods, Instrumentation and Procedures.

Two instructional videos were used for home-based IET. Video 1 included a short (<5 minutes) segment about the benefits of IET on blood pressure and what participants should expect to experience during IET sessions, which was designed for participants to watch just once during their initial exercise session. The second video was a step-by-step, timed instructional video guiding participants through the IET protocol. Participants were encouraged to watch the second video each time they completed a "home-based" IET session. The videos were accessed through a private YouTube, which only the research team and participants could view. Videos were used to provide exercise participants with visual and auditory feedback along with an on-screen timer, to ensure completion of the protocol. During an orientation session, all participants received detailed instructions from research team members on the use of their equipment and what to expect from a typical IET session, before leaving the laboratory**.**

Isometric Exercise Training (IET)

The LAB IET group participated in a group (~4 participants per session) exercise program, led by a member of the research team, three days per week for 12 weeks, followed by 6 weeks of monitored detraining. The HOM IET group completed the same IET program, alone in a location of their choice (e.g. home), following the instructional training video and recorded their performance in a participant pack provided (see Appendix 6). The CON group did not participate in IET during the 18-week study period, but were given the opportunity to participate at the end of 18-weeks (delayed treatment group).

Prior to each IET session, participants (LAB and HOM) completed an MVC test [see chapter 1 General Methods for a detailed description of determining and MVC]. LAB and HOM participants then performed IET, by following the prescribed protocol at 30% of their MVC value as determined on that day. Exercise participants completed IET using their dominant hand only. They undertook IET three times per week for 12 weeks using a handgrip dynamometer provided at the start of the study (Camry, City Industry, California). Each session comprised 4 x 2 minute contractions at 30% MVC with 1 minute rest periods between contractions. Each training session was separated by at least

24 hours. All IET sessions were completed at the same time of day (within 1-2hrs) as the first exercise session.

Research team members evaluated each LAB participant throughout the exercise session to ensure they achieved and maintained the appropriate exercise intensity. HOM participants self-reported their performance during each exercise session using the participant tracking packet (chapter 1, Instrumentation and Procedures, see Appendix 6). CON participants were asked to maintain their usual daily activities and not to change their current or ongoing physical activity outside the study. Both HOM and CON participants received weekly email communications from the research team members to inquire about changes in medications, illness, and diet that may have occurred during each of the 6-week testing periods (6, 12 and 18 weeks) between laboratory visits.

Data Collection

Resting Blood Pressure Assessments

We measured RBP and HR for all participants at baseline and every 6 weeks thereafter in the laboratory following standard procedures [Pickering et al. 2003,2005; see chapter 1. General Methods for a detailed description of measuring RBP]. An automated BP sphygmomanometer (American Diagnostic Corporation, Adview® 9000 Hauppauge, NY) was used to measure RBP and HR as described in chapter 1.Instrumentation and Procedures. Baseline blood pressure data was recorded from all participants over two days, separated by a minimum of 48 hours. In the event that the resting measures were 10 mmHg different between days, a third day of measurements was completed. All subsequent blood pressure assessments during the study were completed at the same of day (within 1-2 hours) as baseline blood pressure assessments, to account for circadian variation [see chapter 1. Instrumentation and Procedures].

Every 6-weeks and prior to IET in exercise participants the blood pressure cuff was placed on the non-dominant arm and the participant rested quietly for 15-minutes in a darkened, temperature-controlled room (in the seated position with the arm at heart level). During data collection sessions, blood pressure was measured twice, each separated by 5 minutes. An average of the two measures was used for analysis at each time point. In the event that measures 1 and 2 were greater than 10 mmHg different from one another, a third measurement was recorded. If blood pressure was confirmed to be greater than 10 mm Hg following the third measurement, participants were asked to return for subsequent testing 24 hours later to confirm measures. Prior to each assessment visit, participants were asked to consume only water (2 hours prior), abstained from caffeine and alcohol (12 hours prior) and to refrain from participation in vigorous exercise (24 hours prior) to data collection.

Statistical analysis

All data were analyzed using SAS statistical software (SAS Institute Inc., Cary, NC) and GraphPad Prism Software (GraphPad Software Inc., La Jolla, CA). Data are reported as mean and standard error of the mean (SEM). All baseline RBP measures were assessed for differences between groups using a one-way analysis of variance (ANOVA). Comparisons between group means for SBP and DBP and HR were analyzed at baseline (before training) and over the course of 12 weeks of the training and detraining (18-weeks) using two-way repeated measures analysis of variance (ANOVA). P values <0.10 were considered statistically significant for differences between groups.

From data that produced significant results, the Bonferroni post-hoc test was used to show significant differences between means.

Individual participant analyses were further completed using a general linear model. Regression coefficients were calculated and analyzed at each time point (baseline, 6-weeks, 12-weeks, and 18-weeks). Furthermore, recent evidence suggests that pre-training SBP level may be related to IHG training effectiveness, meaning that the higher baseline SBP, the greater the reduction in SBP observed [Millar et al. 2007]. Secondary analyses were conducted based upon a baseline blood pressure of ≥130 or 80 to test for and address such an association.

Results

Effects of 12 weeks of isometric handgrip training on resting blood pressure

No significant difference in mean blood pressure reductions was found between groups (e.g. CON versus HOM or LAB). While significant between groups, reductions in group mean blood pressure were found at week 12 (9.1 ± 4.1 mmHg; p <0.10) following LAB-based (8.3 ± 4.4 mmHg; p <0.10) and HOM-based (9.7 ± 3.4 mmHg; p <0.10) IET (Table 10). Changes in DBP were not significant for either LAB (2.78 ± 2.2 mmHg) or HOM (2.16 ± 2.0 mmHg) groups after the training period. Secondary analyses in participants with blood pressure ≥130 or 81 mmHg exhibited more considerable reductions in SBP at 6 and 12 (-9.1 ± 5 and -13.1 ± 4mmHg (P<0.10) after training in the laboratory. This reduction was also maintained for 6 weeks after cessation of training (-9.05 ± 6 mmHg; P <0.10; Table 10). In participants with an initial RBP of ≥130 or 81 mmHg, reductions in SBP were also observed in the home-based training group (HOM) upon completion of the training (at week 12; -11 ± 4 mmHg; P <0.10) (Table 10).

Surprisingly, reductions in diastolic blood pressure were observed at 12-weeks, in the control group only (-7.7 ± 1.2 mmHg; $P < 0.10$; Table 10) but did not persist during detraining.

Effects of 12-weeks of isometric handgrip exercise on resting blood pressure maintenance during 6-weeks of detraining

Despite no longer participating in IET, reductions in SBP observed as a result of participation in 12-weeks of IET were sustained below baseline SBP after 6-weeks of detraining. In LAB and HOM groups, SBP was 8.3 ± 4.5 mmHg and 5.5 ± 3.4 mmHg lower than baseline respectively at week 18. Furthermore, while not significant, there was a trend for DBP to be lower than week 12 compared to baseline measurements in both LAB (4.0 ± 2.9 mmHg) and HOM groups (5.5 ±1.8 mmHg). Neither SBP (0.61 ± 2.3 mmHg) nor DBP (+0.96 ± 1.1 mmHg) were significantly lower than baseline between 12 and 18 weeks in control participants.

Compliance and Adherence to Exercise Protocols

Attendance at exercise sessions in the LAB group and self reported sessions in the HOM group varied during the training period, but the HOM group reported a decrease in participation from 100% - 90% during the first 6-weeks, to 90% - 74% in the last 6-weeks. Five of the LAB participants completed less than three sessions per week in the last 6 weeks averaging 2 out of 3 completed sessions (66% per week). Overall the average attendance to the prescribed protocols was 81% (29 of 36 sessions; range 50% to 100%) in LAB and 82% (29.5 sessions; range 38% to 100%) in HOM.

Discussion and Conclusions

The present investigation is the first to evaluate the effects of unsupervised home-based IET, utilizing a video-based platform, on laboratory measured RBP. This is one of a few studies to explore the efficacy of home-based IET, which hitherto have mainly involved laboratory-based training programs. It is also the first to employ a three-group design with a direct comparison of laboratory-based IET with home-based IET in otherwise healthy, but hypertensive adults. The primary finding was that 12-weeks of home-based and laboratory-based IET lowered systolic but not diastolic blood pressure compared to control, with no identifiable significance when evaluating reductions in blood pressure between groups**.** Moreover, there were no significant differences in RBP reductions when comparing the HOM and LAB IET groups.

Simply knowing about, and understanding the health benefits of physical activity appears to be an insufficient stimulus for engagement in habitual exercise [Aycock et al. 2015]. Considering the challenges associated with overcoming barriers to participating in exercise interventions, reduced participation could be explained by an interaction between personal, social and environmental factors, which can either encourage or inhibit an individual from participation [Zimmerman et al. 2016]. Thus, it is important that exercise like IET can be completed outside the lab/gym (unsupervised) to combat compliance barriers, including the use of specialized equipment, time and cost [Belza et al. 2004; Gillen and Gibala 2013; Lascar et al. 2014, Trost et al 2002;]. Home-based exercise further eliminates the necessity for regular laboratory or gymnasium visits and associated travel. Moreover, it has been suggested that for some groups of people, home-based exercise is strongly preferred in lieu of group participation [King et al. 1991; Mills et al. 1997; Wilcox et al. 1999].

In review of the literature, emphasis has been placed on the use of home-based training programs to manage and treat chronic diseases and disorders, like HTN [Kuijpers et al. 2013]. However, current data on the efficacy of home-based exercise programs for HTN management is scarce [Farinatti et al. 2016]. Of those reported, the preferred exercise modality has been aerobic training. Farinatti et al. [2005] employed a 4-month walking program, and Hua et al. [2009], 12 weeks of low intensity walking. Both investigations reported reduced RBP (SBP -6 and DBP -9 mmHg; SBP-11±9.4, DBP 5.2±5.9 mmHg, respectively). Similarly, Staffileno et al. [2007] utilized 8 weeks of walking and stair-climbing in African American women with HTN or pre-HTN, and observed a significant 6.4mmHg reduction in SBP. Finally, Farinatti [2016] investigated the effects of a 16-month home-based walking protocol on hemodynamic and metabolic markers (blood lipids) in 22 women diagnosed with HTN. After 16 months of training, significant reductions in SBP (4.5 ± 0.3 mmHg) and DBP (2.5 ± 0.6 mmHg) were observed.

There are few studies investigating the effects of home-based exercise programs on blood pressure and even fewer utilizing IET for BP control as outlined previously. For example, two modalities have been used, including IHG [Goessler et al. 2018], like that of the present study and isometric wall squat exercise [Wiles et al. 2017]. Wiles et al. [2017] used a novel wall squat training program for 4 weeks in a randomized crossover design and observed significant reductions in resting SBP (4 ± 5 mmHg) and DBP (3 ± 3 mmHg). Shortly thereafter the same researchers published a second study further validating their protocol for home use [Wiles et al. 2018].

However, wall squat exercise places significant stress on the knees, hips and lower back and requires considerable initial muscle strength. It also requires balance and coordination. Furthermore the wall squat training of Wiles et al. [2018] requires participants to measure their HR and use a goniometer. It also involves a demanding incremental wall squat exercise test at baseline and subsequent exercise sessions [Wiles et al. 2017; Wiles et al. 2018]. While appropriate for younger able-bodied individuals, this type of training program is unlikely to be appropriate for hypertensive older patients, especially since they often present with significant comorbidities including obesity [Hall et al. 2015], type II diabetes [Cheung ad Li, 2012] and musculoskeletal disorders [Bae et al. 2015]. Moreover, the American Heart Association recognizes IHG as a favorable modality for larger cohort programs given its simplicity and convenience, achieving or exceeding target improvements in reducing BP [Brook et al. 2013].

Using an identical protocol to the present investigation, Goessler et al. [2018] published the first home-based IHG study and observed significant reductions in SBP and DBP over an 8-week period (5 mmHg). However, a direct comparison was made using self-selected home-based aerobic exercise training (avg. ~110 minutes/week) vs. prescribed home-based IHG exercise training (~33 minutes/ week). Changes in RBP were not observed from 24-hour ambulatory BP recordings following IHG [Goessler et al. 2018]. Aerobic exercise training was claimed to be more effective at lowering both resting and ambulatory BP, compared to IHG. However, this is a questionable comparison, given the variation in total exercise volume between study groups (IHG = 33 min/week vs. aerobic training ~110 min/week). A more meaningful approach to further understanding the efficacy of IET (e.g. IHG) as an effective home-based modality, would be a direct comparison between laboratory-based and home-based IHG, similar to that of the present study.

Furthermore, in the study by Goessler [2018], participants reported a loss of interest during the home-based IET, which may have been a factor in the declining compliance (96% at the start of the study and 63% at the end) [Goessler et al. 2018]. These authors utilized a fully programmable ZONA Health IHG device with integrated software. Despite on-screen prompts via the handheld device, combined with monitored telecoaching, this method may have been less visually-appealing and engaging compared to our face-to-face training, resulting in a negative effect on compliance. In the present study, we created an instructional YouTube video in an attempt to mimic face-to-face studies that have promoted a sense of social support, whilst relying on participants to be self-motivated; an important element in successful home-based exercise compliance [Glaros and Janelle, 2001].

Unlike other IET studies [Badrov et al. 2013a,b; Badrov et al. 2016; Bartol et al. 2012], the number of exercise sessions completed by IET training participants was not 100% (LAB 81% and HOM 82%). However, we believe a degree of "personal" engagement and on-screen "social support" via instructional video may have been, in part, responsible for higher average levels of compliance observed in our study (LAB 81% ; HOM 82%) compared to the study by Goessler et al [2018]. We report similar levels of compliance in both LAB and HOM participants, which aligns with similar reductions in RBP across groups. A possible limitation of our study, as well as that of

Goessler [2018], was that the IET protocol did not change throughout the training period. Published recommendations for periodic variation in exercise type, intensity and duration have been linked to increased adherence and interest [Glaros and Janelle, 2001] as a part of home-based exercise strategies. Thus, there is the need to develop an IET program that includes a wider variety of simple isometric exercise modes. . This may prove most successful in encouraging older hypertensive participants to perform isometric exercise in the home.

Limited data exists on the characteristics of RBP changes upon cessation of IET. Few studies have assessed the potential for sustained reductions in RBP during a detraining period ranging from 2-4 weeks [Devereux et al. 2010; Wiley et al. 1992]; and only one study has measured RBP post-IET for an additional 6-12 weeks [see Chapter 2 for supporting discussion and chapter 1 for potential mechanisms responsible for lowering RBP with IET]. Results of the present study are in line with previous data from our laboratory, which indicate that RBP was not only lower but also observed below baseline measures for an additional 6 weeks after cessation of training, despite no longer participating in IET [see chapter 2 for additional observations and supporting data]. This is the second study to identify prolonged reductions in RBP following an extended training and detraining program. Thus, these data may be used in support of longer-lasting training adaptations, as elicited following IET [see chapter 1 and 2]. Additional detraining protocols exploring the mechanisms responsible for these longer-lasting reductions in resting blood pressure following IET, are now required to confirm our results.

Larger randomized trials are still required in order to truly establish the efficacy of IET on a public scale [Brook et al. 2013]. IHG, when prescribed at 30% of MVC 3 days per week for 6-12 weeks in pre-hypertensive and hypertensive adults is an effective modality of exercise to elicit both clinically-relevant and statistically significant reductions in RBP in both laboratory or gymnasium-based and home-based settings [Badrov et al. 2013 a, b; Goessler et al. 2018; Hess et al. 2016b; Taylor et al. 2003]. Wiley et al. 1992]. This is highlighted by data from our lab and others, which suggests a degree of heterogeneity in responsiveness of participants who complete isometric training programs [Badrov et al. 2016; Bartol et al. 2012; Olher et al. 2013; Pagonas et al. 2017; Stiller-Moldovan et al. 2012]. Thus, extrapolating the success of smaller randomized control trials and cohort studies to generalize the effects of IET more broadly, is inappropriate. However, with the success of published trials including the present study, future IHG investigations can be designed and implemented with greater confidence. Simple, cost effective, home-based IET programs can be implemented so as to not only effectively lower RBP but to also be integral to the success of HTN management, reaching a greater population who may be unable to otherwise engage in exercise-based HTN management strategies [Goessler et al. 2018; see chapter 3 IET and co-morbidities].

In conclusion, a 12-week home-based IET program lowered RBP to a similar extent to that of a previously-used laboratory-based intervention, in hypertensive adults. As a result of the present study, home-based IET can be implemented with some confidence, in participant who have a wide range of blood pressure values. The findings of the present study also demonstrate that longer training programs can induce sustained post-training reductions in RBP, especially in those with HTN, (i.e. a training effect).

These findings support the implementation of community-based exercise programs to combat high blood pressure, which is a known risk factor for cardiovascular disease.

Tables:

Table 9. Participant demographics.

Values are means ± SEM. CON: control; LAB: lab-based IET; HOM: home-based IET; BMI: body mass index; HTN: hypertension

Group	N	Male (N)	Female (N)	Age (mean)	BMI (mean)	HTN >130 or 81 mmHg	HTN Medication
Control	5	2	3	47 ± 9 yrs.	27 ± 7	N = 4	N = 4
LAB	7	2	6	53 ± 5 yrs.	26 ± 6	N = 2	N = 8
HOM	9	2	7	47 ± 12 yrs.	25 ± 5	N = 6	N = 8

Table 10. Participant resting blood pressure at weeks 0 (baseline) and week 18 detraining.

Group		BL (week 0) mean ± SEM	6-weeks mean ±SEM	12- weeks mean ± SEM	Detraining (18-weeks) mean ± SEM
CON	SBP (mmHg)	137 ± 4.5	134.4 ± 3.9	134.7 ± 4.2	136.4 ± 2.3
	DBP (mmHg)	86.8 ± 3.4	82.8 ± 3.2	78.7 ± 3.7	87.8 ± 1.2
LAB	SBP (mmHg)	137.6 ± 3.7	131.3 ± 3.3	128.5 ± 4.1	129.31 ± 2.9
	DBP (mmHg)	87.1 ± 3.2	85.8 ± 2.5	84.3 ± 2.1	83.1 ± 2.9
HOM	SBP (mmHg)	137.7 ± 4.1	129.7 ± 5	128.0 ±3.4	132.2 ± 3.4
	DBP (mmHg)	88.4 ± 0.8	82.8 ± 1.5	81.6 ± 2.0	83.8 ± 1.8

Values are means ± SEM (CON group n = 5; LAB group n = 7; HOM group n = 9) SBP: resting systolic blood pressure; DBP: resting diastolic blood pressure.
* *P* value < 0.10 ** *P* value <0.05

Figures:

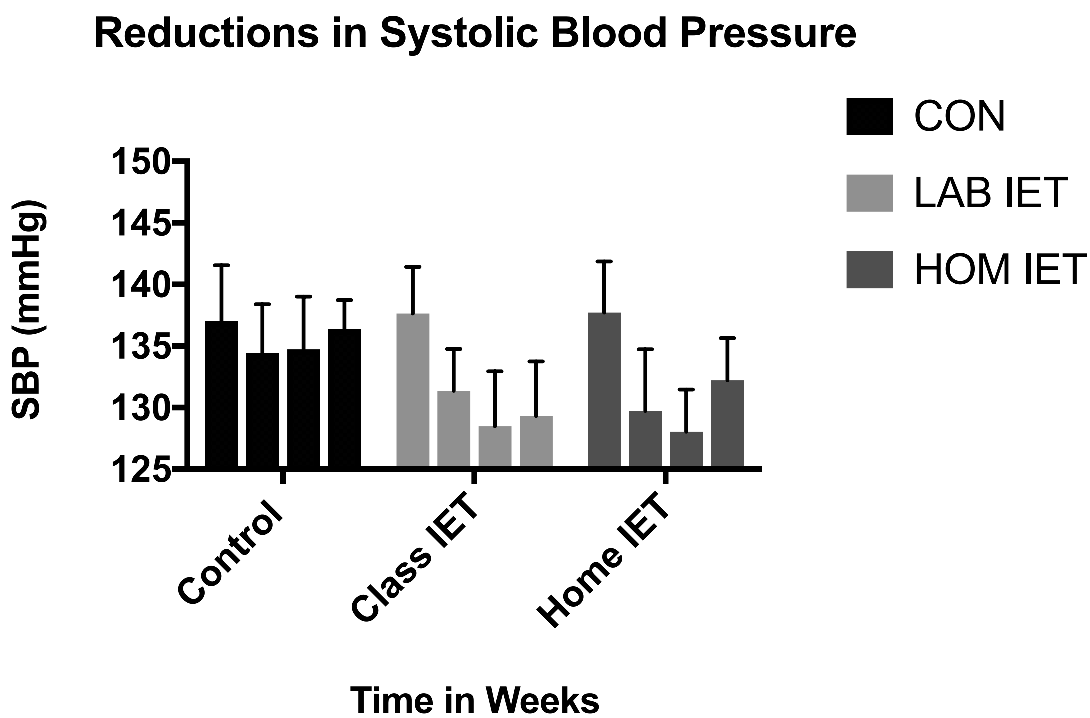

Figure 25: Overview of changes in resting SBP between groups; weeks 0 vs. 18 (i.e. training period). *p<.10

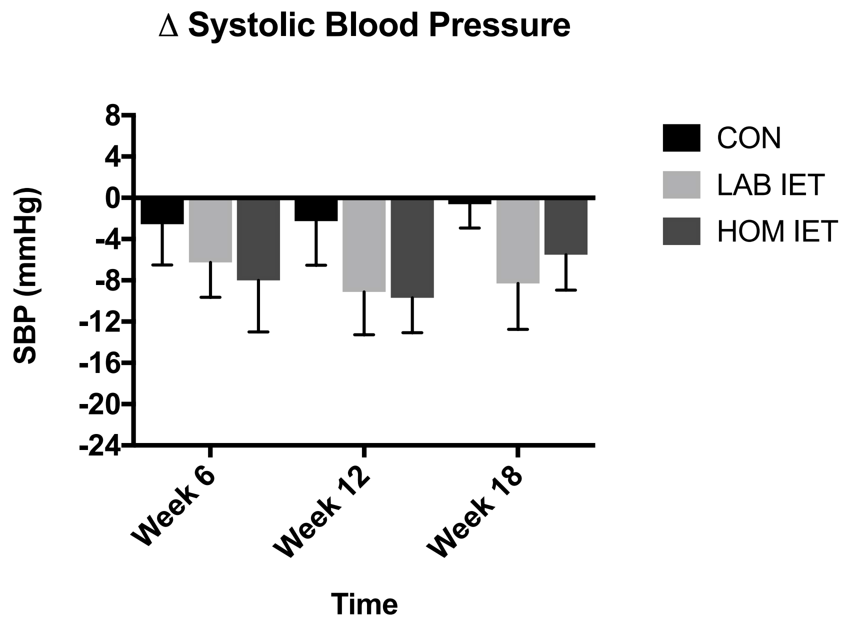

Figure 26: Delta (Δ) difference in resting SBP across all three groups. Difference is relative to baseline (week 0). *p<.10

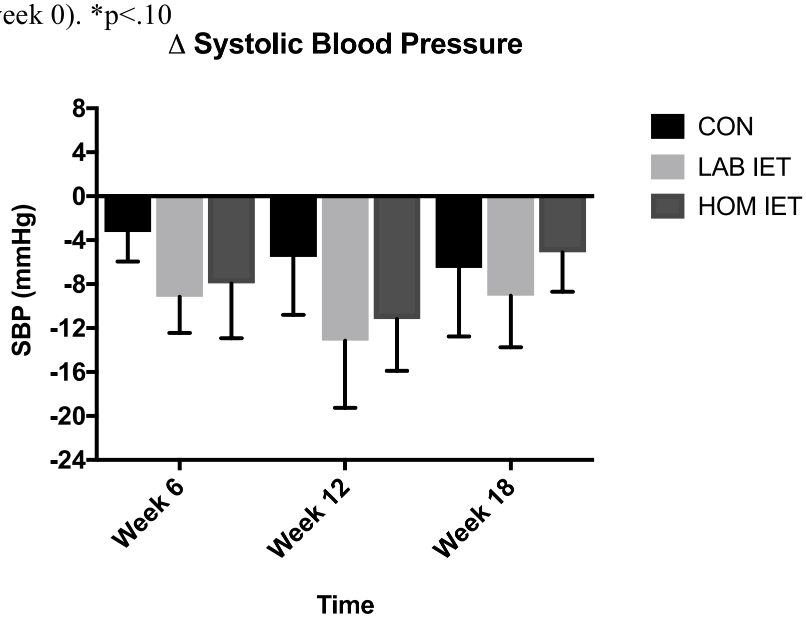

Figure 27: Delta (Δ) difference in resting SBP across all three groups including **RBP restricted to participants with baseline RBP 130/81** and above. Difference is relative to baseline (week 0). *p<.10

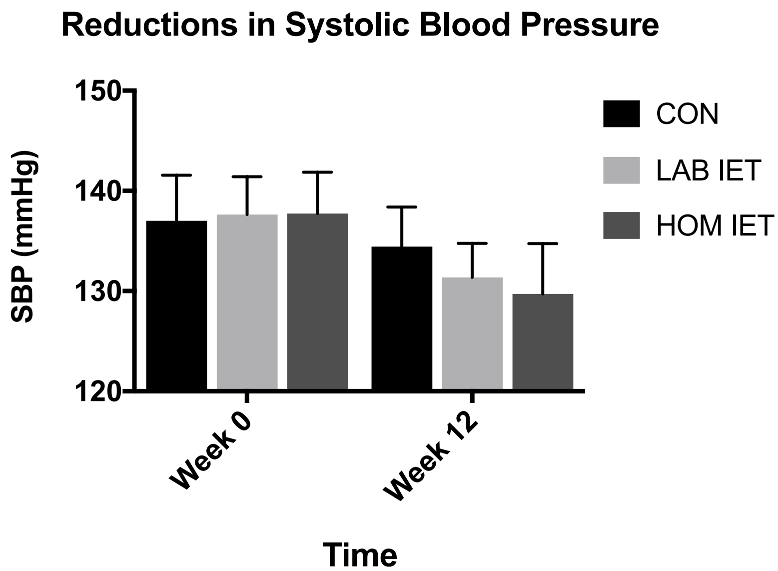

Figure 28: Overview of changes in resting SBP between groups; weeks 0 vs. 12 (i.e. training). *p<.10

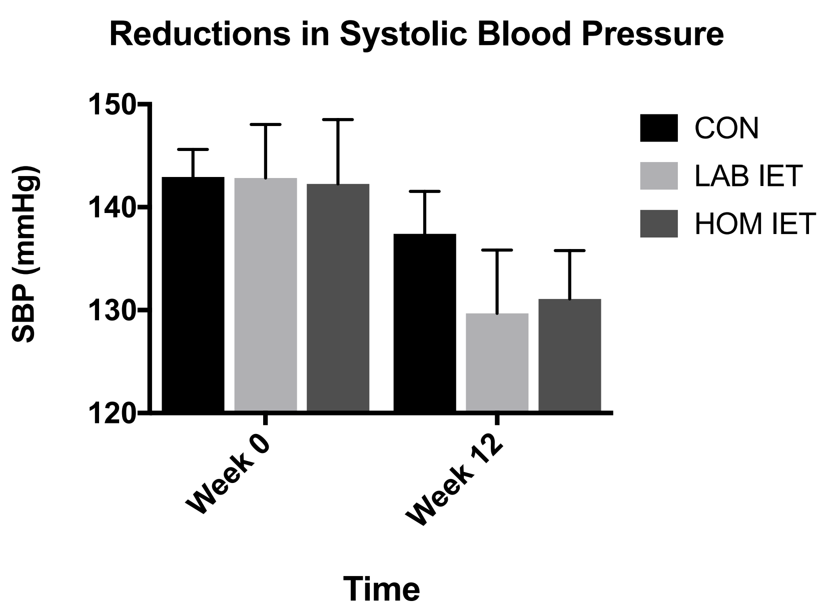

Figure 29: Overview of changes in **resting SBP between group restricted to a RBP of >130/81 mmHg**; weeks 0 vs. 12 (i.e. training). *p<.10

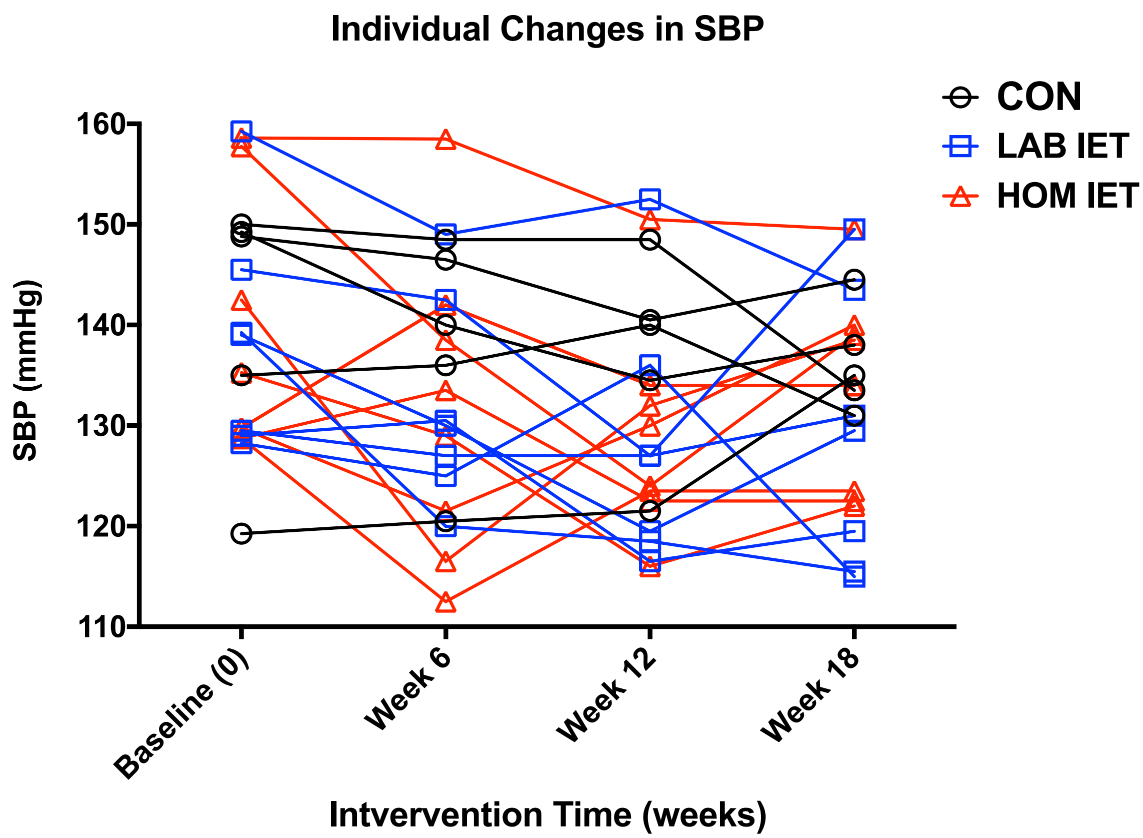

Figure 30: Individual participant responses from week 0 (baseline) to week 18 (detraining).

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CHAPTER 5: THE EFFECTS OF VASOACTIVE BLOOD MARKERS, INFLAMMATION, AND MUSCLE MASS IN ISOMETRIC EXERCISE TRAINING INDUCED REDUCIONS IN RESTING BLOOD PRESSURE

Abstract

Purpose: IET is an effective supplemental mode of exercise for the management of RBP; however, mechanisms responsible for training adaptations have not yet fully been identified. Isometric contractions reduce blood flow as a result of vascular compression thus altering muscle metabolism. In response, active muscle could increase the production and circulation of vasoactive molecules (e.g. VEGF) and alter inflammatory biomarkers (IL-6 and TNF-α), which may lead to adaptations in resistance vessels. Methods: We investigated the influence of bilateral arm or leg IET on plasma VEGF, IL-6, and TNF-α at three different time points over the course of 6-weeks. 17 apparently healthy and recreationally active normotensive males (19-25 years) were randomized to one of three conditions; double bicep curl (IBC) IET, double leg extension (ILE) IET or control (Con). IET groups completed exercise sessions at 15% maximal voluntary contraction three days per week for 6-weeks. Changes in RBP were assessed 3 days per week each week. Venous blood samples were collected at baseline and every three weeks; before exercise, 1 hour after the start of exercise, and 24 hours post exercise. The control group performed identical procedures without exercise. Results: 6-weeks of IET lowered group mean SBP (IBC -6.0 ± 1.2 mmHg $p = 0.007$; ILE -5.35 ± 1.6 mmHg $p=0.019$); No significant changes in control participant SBP (0.96 ± 3.61 mmHg) or DBP (-1.77 ± 1.99 mmHg) was observed ($p>0.05$). No significant differences were observed in VEGF, IL-6 or TNF-α at any time point during the intervention ($p>0.05$). Conclusions: 6-weeks of bilateral arm and leg IET significantly lowered RBP in normotensive adult

males but RBP adaptations were not accompanied by changes in circulating VEGF, TNF-α and IL-6. These data may also suggest that RBP adaptations may occur independent of muscle mass.

Introduction

IET is now recognized and recommended by both the American Heart Association and American College of Cardiology [ACC Guidelines 2017; AHA Guidelines 2017 - Whelton et al. 2017]. Despite a general success the precise mechanism(s) eliciting reductions in RBP remain largely unknown [Brook et al. 2013; Lawrence et al. 2014; Millar et al. 2013; Whelton et al. 2017]. Hess and Smart [2017] propose a novel alternative inspired by remote ischemic conditioning (RIC) whereby IET adaptations may be occurring via systemic blood factors, produced during physiological ischemic training (PIT) [Epps et al. 2016; Hausenloy and Lim, 2012; Hausenloy and Yellon, 2008; Iadecola and Anrather, 2011 ; see chapter 1,Supportive Evidence for Systemic Biomarkers as a Mechanism of IET].

PIT refers to brief bouts of ischemia induced by isometric muscular contraction and subsequent reperfusion of muscle during rest periods [Ni et al. 2015]. This initiates a protective phenotype by stimulating endogenous pathways in distal organs and tissues [Edwards et al. 2007; Hess and Smart, 2017; Ni et al. 2015; Ni et al. 2017; see chapter 1]. The mechanisms likely responsible for proposed adaptations include up-regulated vascular endothelial growth factor (VEGF) mRNA expression, circulating VEGF protein and angiogenesis following intermittent bouts of muscle ischemia [Ji et al. 2007; Lin et al. 2012, 2014; Patterson et al. 2013; Shweiki et al. 1992; Ziche et al. 1997].

4-weeks of PIT in rabbits applied 8 times per day, up-regulated circulating VEGF protein and angiogenesis in contralateral ischemic limbs [Shen et al. 2009; Zhao et al. 2001]. A single published trial of PIT using handgrip exercise at 100% MVC (1 min contractions, 20 reps, 1 set in each hand, 2x daily, for 3 months), significantly increased VEGF protein in patients with coronary artery disease and augmented collateral blood flow in the intact myocardium [Lin et al. 2012; 2014]. These results suggest locally produced but systemically protective angiogenic pathways were activated [Epps et al. 2016; Hausenloy and Lim, 2012; Hausenloy and Yellon, 2008; Iadecola and Anrather, 2011, see chapter 1 for detailed discussion]. Modifications within resistance vasculature via angiogenic pathways could lead to enhanced vessel density, lowered total peripheral resistance and reduced BP [Edwards et al. 2007; Hess and Smart, 2017; Levy et al. 2001; Shimizu et al. 2016].

HTN is associated with a degree of chronic low-grade inflammation and endothelial dysfunction according to compiled data in several review articles [Chrissbolis et al. 2011; Dinh et al. 2014]. Published work has also shown pro-inflammatory cytokines (e.g. interleukin-6: IL-6, and tumor necrosis factor- α: TNF- α) have been implicated in HTN progression [Bautista et al. 2005; Chamarthi et al. 2011; Fernandez-Real et al. 2001; Naya et al. 2007]. Habitual exercise is known to play a role in suppressing the inflammatory cascade by stimulating endogenous anti-inflammatory cytokines (IL-1a and IL-10) and enhancing endothelial nitric oxide bioavailability [Goto et al. 2003, 2007; Petersen and Pedersen et al. 2005; Smart et al. 2011; Steensberg et al. 2003]. Furthermore, anti-inflammatory effects are evidenced by lower levels of circulating IL-6 and TNF-α following exercise [Goto et al. 2003, 2007; Petersen and Pedersen et al. 2005;

Smart et al. 2011; Steensberg et al. 2003]. Conversely, IL-6 has been described an anti-inflammatory myokine, or muscle derived cytokine, which directly inhibits TNF-α production [Petersen and Pedersen, 2005]. However the anti-inflammatory potential of IET has received little attention.

Obstruction of vascular conductance, observed during isometric contractions, may be one of the most important aspects of IET driving RBP adaptations, which aligns with the premise of PIT and RIC [Hess and Smart, 2017; Hausenloy and Lim, 2012; Mitchell and Wildenthal, 1974; Sjogaard et al. 1986] Both intervention strategies closely resemble IET, whereby they are performed for several repetitions several times per week. Albeit less profound, relative to IET, ischemia training (RIC & PIT) can independently lower RBP (-6 mmHg SBP; -3 DBP mmHg) for periods of 7 to 10 days [Madias and Koulouridis, 2014; Madias, 2015].

Past work suggests MVC intensities of 10-30 % are adequate to induce periodic and reversible tissue ischemia via occlusion of arterial inflow [Baross et al. 2012; Humphreys and Lind 1963; Gaffney et al. 1990; Hess et al. 2016b; Lind and McNicol, 1967; Lind et al. 2011; Sjogaard et al 1986; Wiles, Coleman, and Swaine 2010]. Prospectively, improvements in TPR and architectural adaptations of resistance vessels are a viable candidate for IET induced reductions in RBP [Hess and Smart, 2017]. Furthermore, several review articles have reported conflicting evidence regarding importance of muscle mass exercised during bouts of IET [Lawrence et al. 2014; Millar et al. 2014] and therefore the importance of muscle mass as a dependent variable for lowering RBP is unresolved.

Methods

This study was a randomized controlled trial design with three groups. The study was a total of 9-weeks with a 3-week acclimatization period, followed by 6-weeks of an isometric intervention. Participants (chapter 5, Table 1) were recruited from the student body of the University of North Carolina at Charlotte and gave written informed consent prior to their enrollment in the study. The University of North Carolina at Charlotte's Institutional Review Board and Institutional Biosafety Committee approved all procedures for the study

Participants

60 male subjects underwent a rigorous prescreen to determine eligibility; 17 total participants met our inclusion criteria (Table 11). Inclusion criteria included males only; UNC-Charlotte undergraduate or graduate students; at least 18 years of age; no physical limitations in the subjects legs or arms that would prevent them from completing isometric contractions; a resting blood pressure between <130 mmHg systolic/ <81 mmHg diastolic and > 90 mmHg systolic/ >70 mmHg diastolic. See chapter 1. General Methods, Participants for detail on inclusion and exclusion criteria.

Procedures and Data Collection

Dual Energy X-ray Absorptiometry (DEXA)

Prior to the start of exercise all participants underwent a DEXA (GE Lunar Primo Prodigy, with Encore 2011 Version 15 integrated software; Madison, WI) evaluation to assess lean tissue mass (muscle) and total/regional body fat mass.

Resting Blood Pressure Assessments

An automated BP sphygmomanometer (American Diagnostic Corporation Adview® 9000, Hauppauge, NY) was used to evaluate RBP and heart rate (HR). See chapter 1. General Methods for detailed description of automated blood pressure assessments] Baseline BP data was recorded from all participants 3 measures per day, 3 days per week for 3 weeks prior to the intervention period (27 pre-exercise measures). Three weeks was used for acclimatization and to account for reductions in RBP simply due to familiarity with test procedures and to standardize an accurate baseline for each participant during the pre-training period [Peters et al. 2006; see chapter 1. General Methods for detailed discussion of RBP evaluations].

Procedures for measuring blood pressure have been described previously [see chapter 1, General Methods]. All blood pressure assessments were completed at approximately the same time for each collection (within 1-2 hours). During the intervention period measures were collected twice in a single sitting separated by 5 minutes. An average of the two measures was used for analysis at each weekly time point (~6 measures/week)..

Maximal Voluntary Contraction (MVC) Measurements

A series of MVC's were completed prior to the exercise session each day. Subjects were seated and asked to complete three short (5-second) maximal arm bicep curl or leg extension contractions with both limbs using an isokinetic dynamometer; Biodex® [see chapter 1 General Methods for a detailed discussion of determining an MVC]. The highest of three MVCs was recorded.

Isometric Exercise Training

Each exercise session required subjects to perform 2-minute isometric contractions at 15% MVC (established that day) in their the arms or legs, with 1-minute rest between contractions, repeated 6 times. Each exercise session lasted approximately 20 minutes including preparation, MVC, and protocol completion.

Isometric Double Bicep Curl Training (IBC)

Subjects were seated and appropriately restrained in the isokinetic dynamometer (Biodex® System 4 Pro). The IBC group participated in an exercise training program for 6- weeks (3 times/week). For both the MVC test and exercise session subjects pulled against a fixed 90° modified bicep curl bar with both arms (chapter 1. Figures 5 and 9). Participants completed exercise at the same time of day within 1 hour of baseline over the course of the training period. Subjects performed IET following the prescribed protocol at 15% MVC.

Isometric Double Leg Extension Training (ILE)

Subjects were seated and appropriately restrained in the isokinetic dynamometer (Biodex® System 4 Pro) for leg extension exercise. Following an identical protocol previously described, ILE subjects pushed against a modified leg extension bar with both legs at a fixed knee joint angle of 90° (chapter 1 Figures 4 and 9). Research staff observed each participant throughout their exercise sessions to ensure they achieved and maintained the appropriate exercise workload.

Borg Rating of Perceived Exertion (RPE)

Borg RPE is a way of measuring intensity of physical activity on a scale of 6 (no exertion at all) to 20 (maximal exertion). This measure is participant specific (i.e. perceived effort) and is based on the sensations a subject experiences during an activity. RPE was assessed in exercise group participants only. Subjects were instructed on the use of the Borg scale and asked to identify perceived exertion in the last 5-seconds of each 2-minute isometric contraction (i.e. x6).

Brachial Venous Blood Collection

An experienced phlebotomist collected 10mL of blood from a vein in the antecubital fossa of the non-dominant arm of each participant regardless of study group at specified time points. Details pertaining to blood draws were described previously, in chapter 1, General Methods. For IBC and ILE participants, blood was collected at baseline after 20 minutes of seated rest, 1) immediately before the exercise session, 2) 1 hour after the start of exercise and 3) 24 hours after. Control participants' blood was collected at baseline after 1) 20 minutes of seated rest, 2) 20 minutes later and at 3) 24-hours. Participants underwent a total of 9 blood draws over the course of the study with three draws at 0, 3, and 6 weeks of training. Regardless of group all blood was collected-12 hours post-prandial.

Biological Assays

Commercially available electrochemiluminescence (ECL) immunoassays for determining VEGF, IL-6, and TNF-α concentrations in human plasma were purchased from Meso Scale Discovery (MSD – Rockville, MD). The assays were performed in accordance with Manufacturers instructions and plates were read using a Meso QuickPlex SQ 120 with Discovery Workbench 4.0 integrated software [see chapter 1, Procedures].

Statistical analysis

Variables are expressed as mean and standard error of the mean (SEM). Initial group analyses were conducted by two-way repeated measures analysis of variance (ANOVA). To test for possible heterogeneity RBP we assessed individual responsiveness to IET by regression coefficients using a general linear model. Linear regression analyses of both whole group and individual changes in RBP were generated and analyzed using mean regression coefficients for each group. We tested for a treatment x time interaction. For blood markers, analysis was performed in slices for Control and each exercise group respectively; Control vs. IBC, Control vs. ILE, and IBC vs. ILE. An unpaired t-test was used to assess differences in baseline characteristics between groups. For each subject, each factor (e.g. VEGF) within each group a difference value was calculated at baseline, week 3, and week 6. A two way repeated measures analysis of variance (2 groups vs. 2 measurement points was used (condition x time) for each of the blood factors.

Interactions were assessed and for a significant F ratio, post hoc analysis was completed with sequential Bonferroni. We further examined the effect of IHG training for 6-weeks on the release of selected vasoactive factors and markers of inflammation relative to proposed reductions in RBP. Statistical significance was set at $P \leq 0.05$.

Results

All IHG participants completed 100% of their respective exercise interventions (18 total sessions). Resting BP and HR along with vasoactive and inflammatory biomarker analysis was performed in all 17 participants. One, week 6, 24-hour post-exercise blood draw could not be completed in a single subject due to vascular compliance issues.

The effects of 6-weeks of isometric bicep curl or isometric leg extension exercise training on resting blood pressure.

Reductions in resting SBP and DBP were not significantly different between control and IET groups (p>0.05). Resting SBP was lowered in both arm (IBC) and leg (ILE) conditions following 6-weeks of IET in normotensive males (-6.0 ± 1.2 mmHg p= 0.007; -5.74 ± 1.6 mmHg p=0.019; Figures 33, 34, 36 a and b). The magnitude of SBP change was not significantly different (p=0.882) between arm and leg IET, achieving an equivalent response (Figure 33). No significant reductions in DBP were observed in arm (1.1 ± 3.2 mmHg p>0.05) and leg (-0.09 ± 1.64 p>0.05) IET respectively (Figure 35). No significant differences in RBP were observed in the control condition for either SBP (0.96 ± 3.6 mmHg p>0.05, Figures 32, 34, 36c) or DBP (-1.77 ± 1.99 p=0.939, Figure 35). Regression analyses illustrated a negative slope in both exercising groups that were statistically significant from week 0 – week 6 (IBC -0.94±0.21, p=0.007; ILE -0.96±0.25, p=0.01). Slopes were not significant for the control group (control 0.28±0.21, p=0.23). No significant differences were observed between groups when comparing control vs. IBC and control vs. ILE.

Acute: Vasoactive and Inflammatory Biomarkers

Following a single session of isometric exercise 6 x 2-min contractions with 1-min rest periods at 15% MVC (week 0), no significant changes were observed in VEGF, IL-6, or TNF-α between baseline 1hour post-exercise or 24 hours post-exercise. No significant changes in any of the blood markers were observed in the control condition. Responses within and between groups are shown in Tables 13-15 and were not significant (p>0.05).

Training: Vasoactive and Inflammatory Biomarkers

Following 6 weeks of IET, no significant change in VEGF, IL-6, or TNF-α was observed comparing baseline with 1 hour post-exercise and 24 hours post-exercise from week 0 to week 6. No significant changes in any of the blood biomarkers were observed in the control condition. The responses within and between groups are shown in Tables 13-15 were not significant ($p>0.05$)

Discussion and Conclusions

The aim of this study was to assess the effects of IET for 6-weeks using either a bilateral arm curl or bilateral leg extension protocol on resting blood pressure and production of systemic vasoactive (VEGF) and inflammatory biomarkers (IL-6 and TNF-α). To the best of our knowledge, this investigation is the first to attempt to identify relationships between systemic biomarkers and reductions in RBP in a randomized three-group design and to investigate the influence of muscle mass exercised at the same relative intensity (15% MVC) on RBP.

6-weeks of low-moderate intensity IET significantly lowered resting SBP independent of muscle mass. Furthermore, we did not observe a significant increase in circulating plasma VEGF or significant changes in plasma IL-6 or TNF-α in either the exercise groups or controls at any time point in the study. These results suggest that 15% MVC is an appropriate stimulus when using bilateral arm curl and bilateral leg extension exercise for lowering RBP, but RBP adaptations were not accompanied by changes in circulating VEGF, TNF-α and IL-6.

IET and Reductions in Resting Blood Pressure

Reductions in RBP observed in this study were in line with previous studies conducted in adults participating in bilateral leg or bilateral arm IET [Baross et al. 2012; Devereux et al. 2010; Gill et al. 2015; Howden et al. 2002; Wiles et al. 2010]. This is only the second study to investigate bilateral arm curl and bilateral leg extension IET in the same study but the first to exercise both groups at the same relative intensity (15% MVC). Howden et al. [2002] observed significant reductions in SBP following 4x 2min contractions, 3x per week for 5-weeks of IET in both bilateral arm curl at 30% MVC (-12 mmHg) and bilateral leg extension at 20% MVC (-10 mmHg). It is likely the intensity (% MVC) of exercise performed led to a greater magnitude of reduction over intervention period compared to the present investigation (6 weeks).

Wiles et al. [2010] reported a decrease of 4mmHg SBP and 3mmHG DBP at ~10% MVC (75% heart rate peak) and a decrease of 5 mmHg SBP and 3 mmHg DBP at ~20% MVC (95 % heart rate peak). Devereux et al. [2010] observed a similar response in as little as 4-weeks also utilizing ~20% MVC (95 % hear rate peak) with reductions of 5mmHg SBP and 3 mmHg DBP observed. This suggests that muscle mass trained is less important than training intensity [Baross et al. 2012; Devereux et al. 2010; Gill et al. 2015; Millar et al. 2014; Wiles et al. 2010].

However, adaptations in RBP have been proposed to occur in a shorter time period when training a larger muscle mass (e.g. bilateral arms and legs, wall squat) [Gill et al. 2015; Howden et al. 2002; Wiles et al. 2017]. Howden et al. [2002] observed a significant reduction in SBP after 3-weeks of IET using a bilateral leg extension protocol. Conversely, in the present study significant reductions in SBP were not observed until week 6 of IET in both exercise groups. Moreover the magnitude of reduction in the present study was approximately 50% less than reductions in RBP measured by Howden et al. 2002 [Howden et al. 2002; 20% double leg & 30% double arm; 15% MVC in the present study].

Systemic Blood Factors and PIT/RIC a model of IET?

Acute bouts of resistance exercise and resistance exercise training are well known to propagate angiogenic responses [Breen et al. 1996; Gavin et al. 2004, 2007; Kraus et al. 2004; Richardson et al. 1999; Ross et al. 2013], which are associated with muscle hypoxia, vascular shear stress and increases in vascular endothelial growth factor (VEGF) [Larkin et al. 2012]. The mechanisms responsible for blood pressure adaptations to IET are not well understood [Lawrence et al. 2014; Millar et al. 2014]. Resistance to blood flow and blood pressure regulation takes place at the resistance vessels; therefore any improvement in total peripheral resistance (i.e. vessel density) is a likely candidate whereby reductions in RBP following IET may arise from [Badrov et al. 2013a; Badrov et al. 2016; Levy et al. 2001; Naylor et al. 2005; Pries et al. 1995; 2014]. Improvements in endothelial function, oxidative stress, and modifications in the vascular architecture have been observed following IET using other means of measurement supporting the likelihood that improvements are occurring via improvements in TPR [Badrov et al. 2013a; McGowan et al. 2006; McGowan et al. 2007a,b; Peters et al. 2006; see Chapter 1, Mechanisms]

We aimed to establish a relationship between systemic blood factors known to be associated with vascular adaptations to exercise training that may also be responsible for RBP reductions induced by IET, which is a physiological ischemic stress [Hess and

Smart, 2017; Ni et al. 2015; Ni et al. 2017]. It has been suggested that IET (a reversible ischemic intervention) could play a role in vascular adaptations at the resistance vessels by inducing an angiogenic cascade [Hess et al. 2016; Lin et al. 2014; Ni et al. 2015; Patterson et al. 2006; Shen et al. 2009; Shimizu et al. 2009; Shimizu et al. 2016; Shweiki et al 1992; Takano et al. 2005; Zhao et al. 2011]. The capacity of an isometric contraction at 10-30% MVC to attenuate intramuscular blood flow by mechanical compression of blood vessels is well established [Humphreys and Lind, 1963; Rowell, 1993]. Reduced muscle perfusion during acute exercise creates a periodic and reversible state of ischemia in exercising tissue, activating the hypoxia inducible factor 1-a – VEGF signaling pathway [Ohno et al. 2012]. Therefore, partial ischemia resulting from isometric exercise may influence oxygen sensitive pathways necessary for exercise adaptations evidenced by enhanced vascular density and lowered TPR [Edwards et al. 2007; Ohno et al. 2012; Wang et al. 2014].

Short-term muscle ischemia has been shown to up-regulate endogenous protective pathways localized to the ischemic tissue but conveying protective effects systemically via vasoactive and inflammatory biomarker expression [Epps et al. 2016; Hausenloy and Lim, 2012; Loukogeorgakis et al. 2005**].** Remote physiological ischemic training has been postulated to elicit cardio protective effects by initiating an angiogenic cascade that has been observed in the contralateral ischemic limb or myocardium [Lin et al. 2012, 2014; Ni et al. 2015; Ni et al. 2016; Shen et al.2009; Zhao et al. 2011].

Therefore, it is reasonable to hypothesize that a single session of isometric exercise and/or 6-weeks of IET regulates VEGF production and modulates inflammatory pathways, thereby enhancing the vessel architecture and lowering TPR. Until now, investigation of vascular growth factors and inflammatory biomarkers following regimented RIC and PIT has been limited to animal studies in rabbits and mice with a few human participant investigations in adults with coronary artery disease (CAD), peripheral arterial occlusive disease (PAOD) and myocardial ischemia [Gao et al. 2011; Lin et al. 2014; Ni et al. 2015; ; Sandri et al. 2011; Shen et al. 2009; Zhao et al. 2011]. In these studies, circulating VEGF was significantly elevated acutely using PIT and RIC techniques. Results of the present study do not at this time align with previous investigations, even though one previous study used isometric handgrip exercise [Lin et 2014].

Lin et al. [2014] employed a 100% MVC protocol (1 min contractions, 10 reps, 2 sets, 2x daily, for 3 months) using handgrip dynamometers and observed significant increases in basal serum VEGF protein, pre (baseline) vs. post intervention (3 months) with subsequent improvements in myocardial collateralization. Importantly, this investigation quantified VEGF by serum analysis; the use of serum may be inappropriate to quantify circulating VEGF levels after exercise [Maloney et al. 1998]. Platelets are known carriers of VEGF [Maloney et al. 1998]. Thus in serum, active platelets release endogenous VEGF, the longer the sample is allowed to sit at room temperature. Lin et al. [2014] did not publish the protocol details of their blood collection and serum extraction.

The majority of IET studies using several different protocols achieved reductions in RBP at intensities ranging from 10 to 30% MVC. The maximal handgrip contractions (~100% MVC) used by Lin et al. [2014] is an important protocol component, which may have partially contributed to the significant VEGF results. Lin et al. [2014] further suggested that true physiologic ischemia training only occurs at intensities >50% MVC and therefore based on this assumption, the intensity of the present investigation may not have been enough to induce a true ischemic stress.

Total volume of exercise regardless of intensity has been discussed in the IET literature [Badrov et al. 2013a]. Comparably, in the present study our participants exercised for approximately 12-min, 3 days per week, for 6-weeks, a total exercise volume of 216 minutes of IET. Lin et al. [2014] participants accrued 720 minutes of training over three months, or an exercise volume 70% greater than the present study at an intensity of exercise that was 35% higher. We suggest that RBP reductions may rely on total exercise volume and intensity of prescribed IET. These variables may be involved with the mobilization of VEGF and other systemic biomarkers.

Described in Chapter 1, HTN is associated with chronic low-grade inflammation and is characterized by 2-3 fold increases in systemic cytokines like TNFα and IL-1β and IL-6 [Petersen and Pedersen, 2005]. Several inflammatory cytokines are associated with HBP, including IL-6 and TNF-a. TNF-a alone is positively correlated with increased BP [Edwards et al. 2007; Ramseyer et al. 2013]. Resistance exercise in particular has been postulated to suppress the inflammatory cascade mostly by production of anti-inflammatory cytokines IL-1ra and -10 according to both original work and comprehensive reviews [Izquierdo et al 2009; Mathur and Pedersen, 2008; Nieman et al. 2004; Stewart et al. 2007]. The highest concentrations of TNF-α are found in skeletal muscle and plasma, especially with adiposity and sedentary lifestyle [Petersen and Pedersen, 2005; Ramseyer et al. 2013]. With relatively healthy participants low levels of basal TNFα likely contributed to a lack of response in the present investigation.

Other resistance exercise protocols (~12-min worth) have induced significant elevations in VEGF especially within 10-min post-exercise that have remained elevated up to 24 hours, utilizing 3 circuits of 15 repetition maximum exercising both arms and legs [Ross et al. 2013]. Past studies of IET have observed that responsiveness to training especially with regard to architectural remodeling may be tied to hypertensive status [McGowan et al. 2007a; b]. Future isometric exercise studies should further explore systemic biomarkers in adults with hypertension instituting an exercise program of both arm and leg IET (isometric handgrip, seated leg extension, or isometric wall squat) to identify the most significant BP and biomarker responses.

Limitations

Retrospectively, our study was not sufficiently powered to identify changes in systemic biomarkers at the time points selected in the present investigation, which was unexpected. The minimum calculated sample size for a power level of 0.80 and an alpha level of 0.05 was 10 subjects per group following a power analysis for our primary endpoint reductions in resting blood pressure, following IET. Due to the non-homogenous biomarker responses to the exercise program a statistically significant difference between time points may have been trending, however a larger sample size would be required to confirm this likelihood with respect to cytokine measurements.

Timing of venous collections is an important variable in these studies. We selected pre-exercise, 1 hour and then 24 hours after the start of exercise for blood collections as significant changes in biomarkers have been reported ranging from immediately post-exercise up to 24 hours after exercise [Gavin et al. 2007; Ross et al. 2013]. With isometric exercise, it is possible the peak systemic biomarker response was not captured, possibly due to a delayed release from muscle [Trennery et al. 2007].

Future work should perform blood draws at 1, 2, 4 and 24 hours to identify post-IET time course.

Conclusions

6-weeks of bilateral arm or leg IET elicited significant reductions in RBP when the same relative intensity was used. The RBP adaptations were independent of muscle mass. Vasoactive and inflammatory biomarkers did not change in this study and therefore were not associated with reductions in RBP. Results may have been influenced by a high level of inter-individual variation in systemic biomarker responses to isometric exercise and IET.

Tables

Table 11. Participant demographics

Group	N	Age	BMI	Upper Body lean mass (kg)	Lower body lean mass (kg)
Control	5	20.8 ± 0.6	22.8 ± 0.7	7.1 ± 0.4	20.2 ± 0.6
IBC	6	21.2 ± 0.2	27.1 ± 1.9	7.8 ± 0.5	20.9 ± 1.0
ILE	6	21.0 ± 0.3	24.9 ± 1.7	7.6 ± 0.5	20.6 ± 1.5

Values are means ± SEM (CON group n = 5; IBC group n = 6; ILE group n = 6) BMI: body mass index; kg: kilogram

Table 12. Participant resting blood pressure

Group		BL (week 0) mean ± SEM	3-weeks mean ±SEM	6- weeks mean ± SEM
CON	SBP (mmHg)	113 ± 0.4	113.0 ± 1.9	114.7 ± 3.6
	DBP (mmHg)	69.2 ± 0.3	68.7 ± 3.4	67.4 ± 1.9
IBC	SBP (mmHg)	119.9 ±0.9	115.2 ± 1.9	113.9 ± 1.2
	DBP (mmHg)	71.8 ± 0.35	69.3 ± 3.4	72.9 ± 3.2
ILE	SBP (mmHg)	117.8 ± 0.4	115.1 ± 1.7	112.1 ± 1.6
	DBP (mmHg)	68.5 ± 0.58	68.8 ± 1.2	68.4 ± 1.69

Values are means ± SEM (CON: Control group n = 5; IBC: Isometric bicep curl group n = 6; ILE: Isometric leg extension group n = 6) SBP: systolic blood pressure; DBP: diastolic blood pressure.* *P* value <0.05 ***P value <0.01*

Table 13. Group vascular endothelial growth factor (VEGF) responses over time.

Group	Time	BL (week 0) mean ± SEM	3-weeks mean ±SEM	6- weeks mean ± SEM
CON	Pre	35.8 ± 11.7	27.7 ± 5.5	23.2 ± 4.4
	Post	29.9 ± 9.2	25.8 ± 6.3	24.5 ± 4.8
	24 hr.	24.9 ± 6.0	25.7 ± 4.3	24.0 ± 4.3
IBC	Pre	38.1 ± 8.9	36.9 ± 8.0	40.4 ± 8.3
	Post	33.0 ± 8.4	37.9 ± 11.0	34.4 ± 7.4
	24 hr.	39.1 ± 6.9	40.4 ± 10.1	43.9 ± 7.4
ILE	Pre	28.31 ± 6.9	27.3 ± 5.1	28.5 ± 27.6
	Post	33.1 ± 8.3	25.3 ± 3.7	27.6 ± 5.4
	24 hr.	26.7 ± 4.8	30.2 ± 7.2	26.4 ± 4.2

Values are means ± SEM measured in pg/mL (CON: Control group n = 5; IBC: Isometric bicep curl group n = 6; ILE: Isometric leg extension group n = 6) CON – pre, 20 minutes and 24 hr. blood draws at 0, 3 and 6 weeks. IET – pre-exercise, post-exercise (45 minutes), 24 hrs. at 0, 3 and 6 weeks. All blood draws following a 12-hour fast

Table 14. Group interleukin-6 (IL-6) responses over time.

Group	Time	BL (week 0) mean ± SEM	3-weeks mean ±SEM	6- weeks mean ± SEM
CON	Pre	1.31 ± 0.98	0.50 ± 0.08	0.38 ± 0.06
	Post	1.30 ± 0.93	0.54 ± 0.08	0.32 ± 0.02
	24 hr.	1.03 ± 0.76	0.38 ± 0.05	0.31 ± 0.02
IBC	Pre	0.47 ± 0.07	0.48 ± 0.06	0.53 ± 0.07
	Post	0.72 ± 0.30	0.50 ± 0.07	0.56 ± 0.06
	24 hr.	0.49 ± 0.11	0.47 ± 0.08	0.43 ± 0.08
ILE	Pre	0.51 ± 0.18	0.55 ± 0.22	0.38 ± 0.04
	Post	0.49 ± 0.13	0.50 ± 0.17	0.34 ± 0.04
	24 hr.	0.81 ± 0.30	0.51 ± 0.21	0.79 ± 0.22

Values are means ± SEM measured in pg/mL (CON: Control group n = 5; IBC: Isometric bicep curl group n = 6; ILE: Isometric leg extension group n = 6) CON – pre, 20 minutes and 24 hr. blood draws at 0, 3 and 6 weeks. IET – pre-exercise, post-exercise (45 minutes), 24 hrs. at 0, 3 and 6 weeks. All blood draws following a 12-hour fast.

Table 15. Group tumor necrosis factor alpha (TNF-α) responses over time.

Group	Time	BL (week 0) mean ± SEM	3-weeks mean ±SEM	6- weeks mean ± SEM
CON	Pre	3.02 ± 0.73	2.51 ± 0.43	2.64 ± 0.35
	Post	2.85 ± 0.67	2.50 ± 0.39	2.62 ± 0.39
	24 hr.	3.06 ± 0.69	2.63 ± 0.47	2.61 ± 0.48
IBC	Pre	2.29 ± 0.25	2.52 ± 0.25	2.47 ± 0.23
	Post	2.24 ± 0.28	2.36 ± 0.19	2.37 ± 0.22
	24 hr.	2.30 ± 0.30	2.50 ± 0.24	2.31 ± 0.16
ILE	Pre	2.30 ± 0.21	3.04 ± 1.02	2.12 ± 0.07
	Post	2.18 ± 0.20	3.49 ± 1.39	2.04 ± 0.05
	24 hr.	4.07 ± 1.80	3.33 ± 1.28	2.72 ± 0.70

Values are means ± SEM measured in pg/mL (CON: Control group n = 5; IBC: Isometric bicep curl group n = 6; ILE: Isometric leg extension group n = 6) CON – pre, 20 minutes and 24 hr. blood draws at 0, 3 and 6 weeks. IET – pre-exercise, post-exercise (45 minutes), 24 hrs. at 0, 3 and 6 weeks. All blood draws following a 12-hour fast.

Figures:

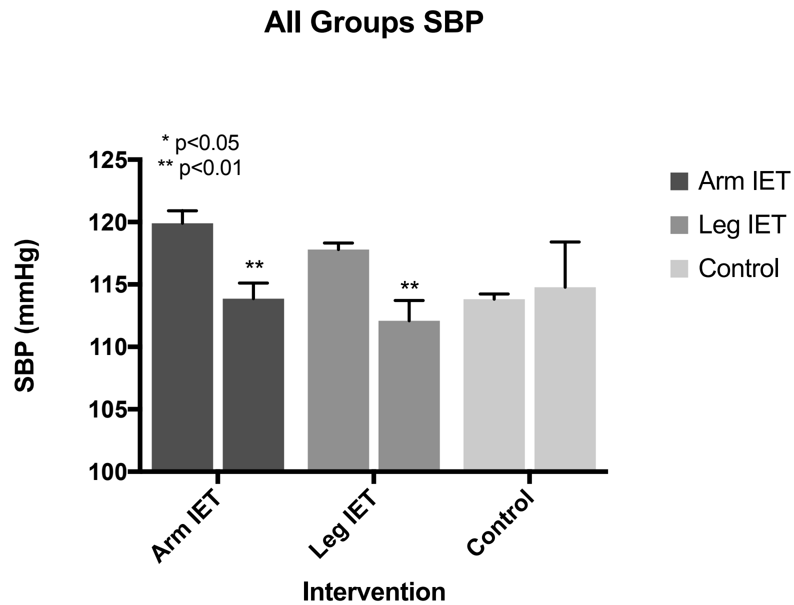

Figure 31: Overview of changes in group mean systolic blood pressure (SBP). All groups, week 0 (baseline) vs. week 6. Exercise groups were not significantly different from each other. *p<0.05; **p<0.01

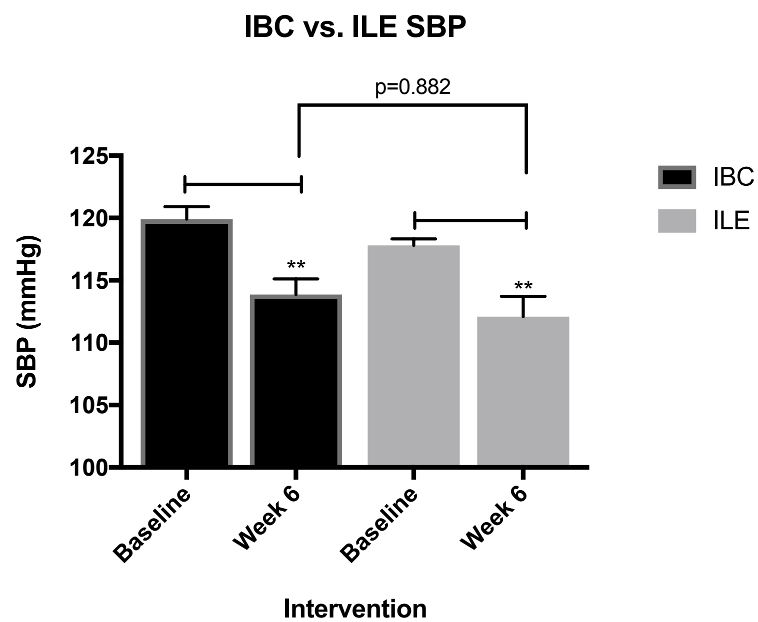

Figure 32: Overview of changes in group mean systolic blood pressure (SBP). Arm vs. Leg IET week 0 (baseline) vs. week 6. Exercise groups were not significantly different from each

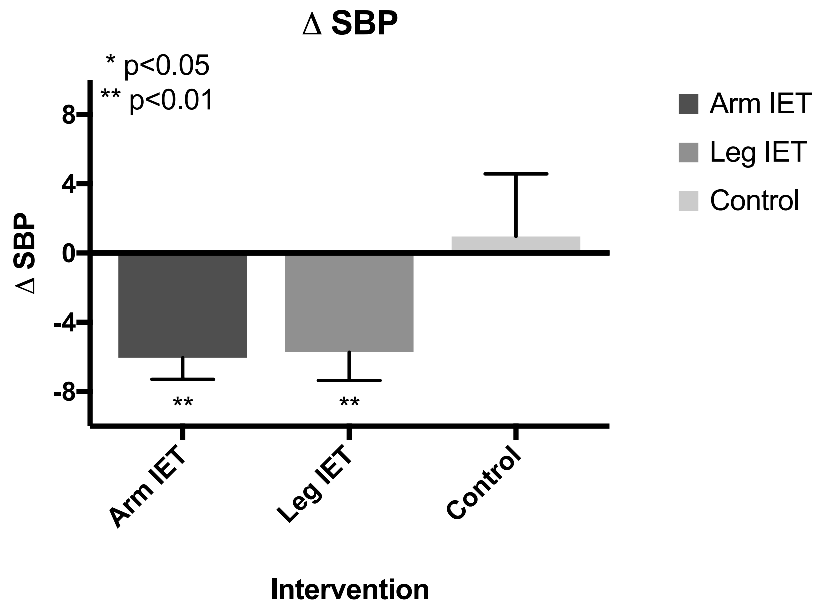

Figure 33: Delta (Δ) in resting systolic blood pressure (SBP) across all groups Week 0 (baseline) vs. week 6.

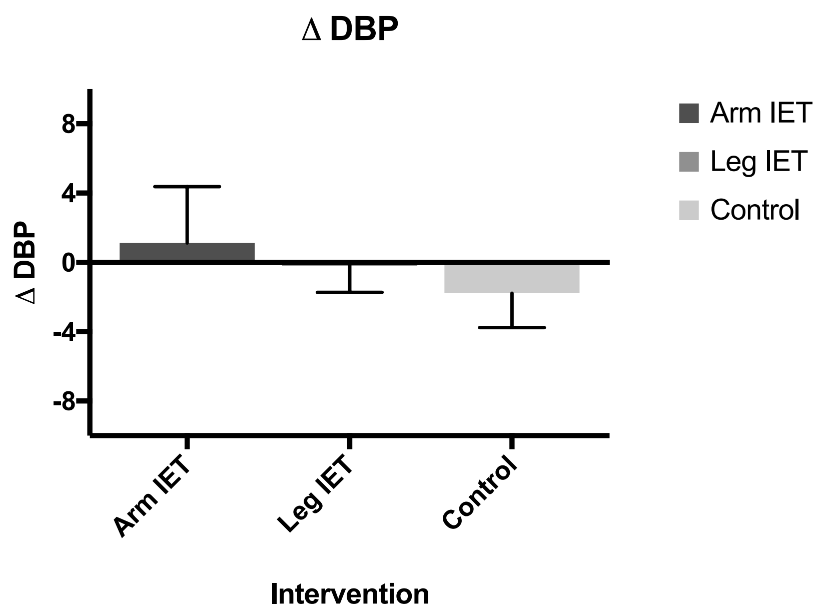

Figure 34: Delta (Δ) in resting diastolic blood pressure (DBP) across all groups Week 0 (baseline) vs. week 6.

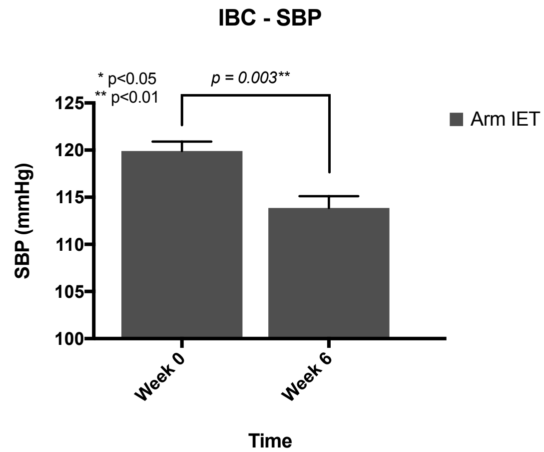

Figure 35a. Overview of changes in group mean systolic blood pressure (SBP). Arm IET, week 0 (baseline) vs. week 6.

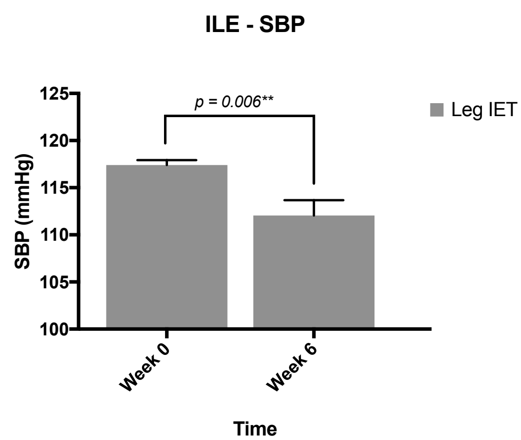

Figure 35b. Overview of changes in group mean systolic blood pressure (SBP). Leg IET, week 0 (baseline) vs. week 6.

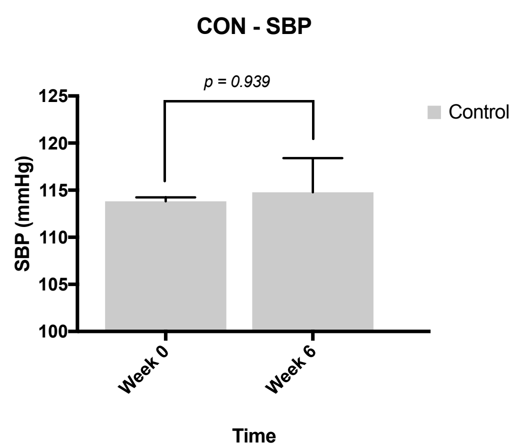

Figure 35c. Overview of changes in group mean systolic blood pressure (SBP). Control, week 0 (baseline) vs. week 6.

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CHAPTER 6: GENERAL DISCUSSION

Executive Summary and Primary Findings

Hypertension (HTN, high blood pressure; >140 and/or >90 mmHg) and its management are critical public health issues, linked to early onset cardiovascular and stroke-related morbidity and mortality [WHO, 2013]. An estimated 1 billion people (~1.5 billion by 2025) worldwide and ~87 million in the United States are affected by HTN [Benjamin et al. 2017]. The last 20 years of IET research has resulted in considerable growth in the area pertaining to alternative strategies for lowering RBP across an array of demographics [Brook et al. 2013]. It has been established through meta-analyses and several comprehensive reviews that, participants who engage in some form of IET exhibit significant reductions SBP, DBP, mean arterial pressure, and PP utilizing several protocols and exercise modalities for periods of 3-12 weeks compared to other forms of exercise [Carlson et al. 2014; Cornelissen and Smart, 2014; see Chapter 2-5].

Introduced in chapter 1, IET refers to short bouts of sustained muscle contractions at a given sub-maximal exercise intensity repeated several times in a single session conducted for several weeks. The primary outcome of IET reported has been significant reductions or modification to hemodynamic variables, including RBP, MAP, and PP. A series of studies led to the discovery whereby IET has grown and is now acknowledged with significant potential as an anti-hypertensive exercise modality for BP control [Brook et al. 2013; Whelton et al. 2017; see chapter 1].

In this dissertation, four main aspects of IET and its effects on RBP have been studied. The aspects involving IET studied were 1) age & cardiopulmonary disease (participant characteristics), 2) training duration with prolonged maintenance effects of training, 3) environment of training 4) and potential mechanistic variables (systemic biomarkers and muscle mass) performed in human subjects. In the proceeding discussion and summary, emphasis will be placed on responsiveness to IET, prolonged adaptations to IET despite a cessation of training, success of home-based IHG, and the exploration of potential mechanisms eliciting observed reductions in RBP.

The main findings reported from these studies include:

1. 12-weeks of isometric handgrip (IHG) exercise not only elicited reductions in RBP but reductions were maintained below baseline measures for an additional 6 and 12 weeks in elderly adults from a local senior center [study 1, chapter 2].

2. IHG exercise can be successfully integrated into an existing cardiopulmonary rehabilitation program, however a small sample size, disease status and polypharmacy may be responsible for a lack of significance in our findings [study 2, chapter 3] indicating that not all participant who engage in IET achieve reductions in RBP.

3. 12-weeks of IHG exercise significantly lowers RBP equally in adults with HBP both in a laboratory face-to-face environment as well as when completed by the participant, alone, outside the lab following YouTube video instruction. Furthermore reductions in RBP were observed below baseline BP for an additional 6-weeks after training had ended, confirming our results from study 1 for maintenance reductions in RBP when monitored for an extended detraining period [study 3, chapter 4].

4. Changes in vasoactive and inflammatory biomarkers did not follow reductions in RBP utilizing a bilateral arm or leg protocol at 15% MVC. These data indicate that in

young adult males, adaptations to IET may be mediated through an alternative mechanism or training regimen [study 4, chapter 5].

State of IET research

Reductions in resting blood pressure and problems regarding patient demographics and medications concurrent with IET

The most common anti-hypertensive effects presented by subjects in this dissertation included reductions in systolic blood pressure (SBP) but not diastolic blood pressure (DBP), no change in either parameter, or a non-significant increase in RBP after training [see chapter 2-5 results]. Results of this dissertation report both in line with as well as conflicting data compared to prior published works.

Regardless of strict data collection guidelines followed [described in Chapter 1], a level heterogeneity in RBP among participants was evident in all studies particularly at baseline. Furthermore, responsiveness to training and several other factors could have influenced our interpretation of the results. For example, when working with older adults, cardiopulmonary rehabilitation patients and those medicated for HBP the variation in RBP at baseline was significant along with polypharmacy [see chapter 3 – Table 2; chapter 3 &4] when participation began. As it was introduced in chapter 2, lowered BP makes up the bulk of the literature, however not all participants completing IET consistently respond to training [Ash et al. 2017; Badrov et al. 2016; Bartol et al. 2012; Stiller-Moldovan et al. 2012; see chapters 2-5] and to date these inconsistencies or limitations of IET are under-reported.

Millar et al. [2014] has illustrated a commonality of reporting in the literature to date; this includes pre and post, group mean reductions in RBP [Carlson et al. 2014; Cornelissen and Smart, 2013; Inder et al. 2016; Millar et al. 2007]. This is simple way to confirm a successful intervention and is published most often. Lacking with this level of analysis is the inter- and intra-individual variability in participants. Closer evaluation of this variation may be more informative for identifying the effectiveness or lack thereof of IET. Among a sample population or in combining all studies, a group analysis may be masking true effects of the intervention. A handful of IET studies report both responders and non-responders to training [Badrov et al. 2016; Bartol et al. 2012; McGowan et al. 2006; Millar et al. 2007; Stiller-Moldovan;] an outcome observed in a number of participants in all 4 studies in this dissertation [See chapter 2-5 individual data].

Furthermore, Millar et al. [2014] emphasizes poor reporting of response rates in past investigations. The evaluation of responders to non-responders is an important measurement when attempting to establish exercise guidelines for IET, which has not yet been done. Only some of this data has been published, which leaves the present evaluation open to estimation only. However, based on the data that is available, success rates of IET could range between 50-83% in participants being treated with antihypertensive medications and between 60-96% in nonmedicated normotensive to hypertensive participants [Millar et al. 2014].

A difference in response rate determined by current pharmacological management is significant [see chapter 2-4]. However at this time, an analysis of any relationship between singular or combinations of antihypertensive medications and a blunted or attenuated RBP response to IET has not been conducted. Outlined in chapter 1, the mechanisms for blood pressure control are multiple, interacting, and responsive to the environment of the individual [Ackermann, 2004; Guyton et al. 2000]. Drug classes of medications known to affect vascular function and regulation directly (e.g. ACE inhibitors) could be overlapping with and blunting the antihypertensive mechanism of action following IET [Lawrence et al. 2014; Millar et al. 2014] or on the contrary eliciting a more robust antihypertensive result.

The likelihood of this is supported by a slightly lowered response rate in those participants taking antihypertensive medications [Badrov et al. 2016; Bartol et al. 2012; McGowan et al. 2006; Millar et al. 2007; Stiller-Moldovan]. We attempted to account for polypharmacy in our data, but due to small samples sizes and the statistical degrees of freedom required to establish such a relationship, we were unsuccessful in the present series of investigations. According to the IET literature the direct effects of medication volume and type prior to participation may have been a confounding variable in our analyses [Chapter 2-4] and must be accounted for in all future studies including medicated hypertensive participants and especially clinical populations [Bartol et al. 2012; Goessler et al. 2016; McGowan et al. 2006; Millar et al. 2013; Stiller-Moldovan et al. 2012].

We especially emphasize the importance for future investigators to consider not only antihypertensive medications but also the current health status of participants along with other demographic variables known to influence HTN. Several of these were discussed at length both with respect to blood pressure, generally, as well as in response to IET [See chapter 1 for detailed discussion] and include age, presence of disease with associated co-morbidities and category of hypertension [Lawrence et al. 2014; Millar et al. 2014]. Two of our studies focused on older adults. The current published literature with respect to age is limited and illustrates mixed responses in men and women over the age of 50 [Bartol et al. 2012; Millar et al. 2008; Ohler et al. 2013; see chapter 2 and 3].

To date, the IET has been assessed with randomized control/cohort studies and the current literature evaluated with meta-analyses and comprehensive reviews [Carlson et al. 2014; Cornelissen and Smart, 2013; Lawrence et al. 2014; Millar et al. 2014]. While we were able to successfully lower blood pressure on average in 50-91% of our participants in each study; a result in line with the majority of published works, these data are hardly generalizable to all persons participating in IET, but are nonetheless informative. In evaluating these data we affirm that individualized programs are necessary to accommodate a wide demographic of responders and non-responders. One method to identify and stratify these data is an independent patient data analysis or IPD. IPD analyses are a way of combining quantitative evidence from related studies that provides a more encompassing view of collected data. These analyses have been especially effective in the area of cancer research for evaluating survival and recurrence following chemotherapy or other treatments [Riley et al. 2008; Stewart et al. 2002]. Riley et al. [2008] suggests this type of evaluation poses numerous advantages over meta-analyses and systematic reviews.

To the knowledge of the author a comprehensive evaluation of individual participant data responses to IET is a critical next step with IET given the broad implications and diversity of modality, protocol design, and inherent variability within and between groups. This is especially important, as investigators should understand the characteristics that define a high responder to a low responder. With this information future studies can provide individualized exercise prescriptions to meet the specific needs of the individual for successful blood pressure control.

The body of literature on IET has reported a general success for lowering RBP but little data has been amassed regarding the relationships of IET and polypharmacy or the number of medications taken concurrently with training [Millar et al. 2014]. Revisiting a prior statistic 17-50% of those already medicated for HBP may not respond to a given IET protocol. Future work should address these issues by developing a scale or a reference range for prescribing IET based on a personal fitness evaluation much like how aerobic and resistance training programs are currently designed [Riebe et al. 2017 – ACSM Guidelines]. For the studies in this dissertation we evaluated individual RBP responses across all four studies as we observed responders and non-responders to IET. Due to small sample sizes variations in our data were especially emphasized in all 4 studies. As a result our observations require additional research to confirm some of our findings.

An evaluation of individual participant data is critical to prescribing IET more broadly. Both aerobic and resistance exercise programs are designed with participant skills and abilities having been considered and specific guidelines for young and healthy or for older and sick populations [Pescatello et al. 2004; Riebe et al. 2017 – ACSM Guidelines]. Therefore, future exercise prescriptions of IET should employ similar methodology for designing individualized isometric exercise prescriptions tailored to meeting the specific needs of the participant, thereby achieving the most efficacious reductions in RBP.

Establishing a home-based IHG program for reducing RBP

The third aim of this dissertation was to determine if IHG exercise utilized in studies 1 & 2 could be effectively implemented into a home-based protocol for community-based effectiveness. The future establishment of IET as a recommended modality of antihypertensive exercise is contingent upon large scale randomized controlled trials [Brook et al. 2013]. Moreover, study 3 was adapted based upon the limitations (recruitment, retention, time commitment) of laboratory based, or center based exercise programs conducted in chapters 2 and 3 alongside the majority of the IET literature in order to combat barriers and improve adherence to exercise whilst achieving appreciable reductions in RBP.

The majority of the IET literature validates the use of low-moderate intensity handgrip exercise to effectively lower resting blood pressure [Badrov et al. 2016; Badrov et al. 2013a,b; Goessler et al. 2018; Millar et al. 2013a;McGowan et al. 2006; McGowan et al. 2007a, b; Millar et al. 2008; Millar et al. 2013a; Taylor et al. 2003; Peters et al. 2006; Wiley et al. 1992; see chapter 2-4]. This contraction style is the most often incorporated of modalities as it is simple and can be completed anywhere with ease [Ray and Carassco, 2003] but prior to this dissertation limited data for its accessibility outside the lab was available. Other modalities such as bilateral leg extension, or bilateral arm curl require expensive and laboratory equipment not readily accessible to the public [Baross et al. 2012Devereux, et al. 2012; Howden et al. 2002; Wiles et al. 2010;]. Moreover, wall squat while more accessible, may not be appropriate for all individuals as it requires considerable muscular endurance and coordination along with knowledge of assessing HR and use of a goniometer.

Regardless of the modality employed, all studies above have been prescribed and under some direction from a research investigator; a likely contributor to the 100% adherence rates that have been reported [Badrov et al. 2013a; Badrov et al. 2016; Badrov et al. 2013b;Wiles et al. 2017; Wiles et al. 2018]. Discussed in greater detail in chapter 4 barriers to exercise are the result of intersecting variables including personal, social and environmental mechanisms that have been reported to both encourage and inhibit exercise participation [Zimmermann et al. 2016; chapter 1 & 3]. Furthermore, cost, equipment access and time required of participants to travel too and from a laboratory facility are significant and impractical for community-based studies [Anderson et al. 2017; Clark et al. 2010; Dalal et al 2010; Fahkry et al. 2011; King et al., 1991; see chapter 4 for a detailed discussion].

Described in chapters 1 and 4 home-based exercise has received special emphasis to combat chronic disease more broadly. Prior to the writing of this dissertation home-based exercise programs, with special emphasis for BP control were extremely limited, and only a handful of studies have been published on the subject [Clark et al. 2010; Farinatti et al. 2005; Farinatti et al 2015; Hua et al., 2009; Staffileno et al. 2007; see chapter 4 for detailed discussion]. Moreover these studies incorporated aerobic and resistance modalities only.

The American Heart Association provides support for handgrip exercise as a preferred modality for community based studies for reasons established previously [Brook et al. 2013]. Home-based training is a necessary next step for combatting HBP at the population level as the number of adults diagnosed with HBP continues to rise [Benjamin et al. 2017]. Furthermore less than a handful of IET studies incorporated home-based exercise either partially or in full for the duration of the intervention. Millar et al. [2013] used IHG 30% MVC 3x/week for 8weeks, however, 30% of sessions were completed independently, the rest under the supervision of the primary investigator. As it was described in chapter 4 mixed visitations likely played a part in adherence and successful BP reductions due to continued contact with investigators [Millar et al. 2013a]. Furthermore, only 2 studies have been published with regard to home-based studies outside the lab entirely, independent of investigator oversight [Goessler et al. 2018; Wiles et al. 2017], only one of which was handgrip exercise [Goessler et al. 2018].

A specialty device company (Zona Health, 2014) has developed and produced a digital handgrip device often chosen for laboratory based IHG [Badrov et al. 2013a; 2013b; McGowan et al. 2006, 2007b; Millar et al. 2013a] and was used in the first home-based IHG study [Goessler et al. 2018]. The device is portable and offers integrative software, helping the participant track each individual session, which can be uploaded for review and evaluated by researchers during training. This device combats current barriers associated with lab-based IHG, as it also provides step-by-step instruction eliminating travel requirements and face-to-face interaction with investigators. Despite these conveniences the devices accessibility is marginalized by a $500.00 market cost [Zona Health, 2014]. Moreover as one investigator has reported, use of the device by participants, was “boring” and did not feel like exercise [Goessler et al. 2018] perhaps due to lack of engagement associated with traditional lab-based IHG [chapter 4]. However it has also been reported that home-based exercise may be a preferred modality over group training, to avoid embarrassment [King et al. 1991; Mills et al. 1997; Wilcox et al. 1999].

Goessler et al. [2018] was the first to report reductions in clinic based blood pressure following IHG at 30% MVC 3x/week for 8 weeks. Moreover their group was the first to report home-based adherence rates or sessions completed outside the lab. As described previously in chapter 4 adherence to training is of the utmost importance for successful training adaptations [Pescatello et al. 2004]. In our study we report a greater level of adherence despite the use of an identical protocol used by Goessler et al. [2018]. We believe this was the result of an interactive YouTube video that led onscreen training carried out by research team members. Additional trials should be conducted to support or refute these observations.

In our study we addressed several limitations of current IHG programs in order to make IHG exercise more accessible and importantly quantifiable and enjoyable. We chose YouTube video as our method of protocol dissemination given that it can be accessed both by computer and smartphone. Moreover, in the event that Internet access was not available detailed written instructions were also provided. Furthermore we identified increased adherence with this methodology as well as similar reductions in both exercise groups participating in IHG. We these data we can confirm that as designed a home-based IHG program can be just as successful to a lab based intervention for lowering RBP.

Maintenance of Reductions in BP and Potential Mechanisms Responsible

Reductions in RBP pressure have been achieved over periods of 3 to 12 weeks and in the case of the present studies maintained below resting pre-intervention levels for up to an additional 6 weeks [see Chapter 2 and 4]. However, several aspects of this intervention remain in question. First, single or multifactorial physiological influences/mechanisms by which reductions in RBP with IET are achieved are still unknown [Lawrence et al. 2014; Millar et al. 2014; see Chapter 1 and 5]. It is highly likely multifactorial mechanisms are involved in adaptations to IET [Hess and Smart, 2017; Lawrence et al. 2014; Millar et al. 2014]. Skeletal muscle afferent stimulation (MSNA)[Choi et al. 2013; Ray and Carassco, 2000; Rondon et al. 2006], and effects of the autonomic nervous system [Millar et al. 2013; Taylor et al. 2003; Wiles et al. 2010] have been suggested to account for reductions in SBP, DBP, and mean arterial pressure = acutely, while improvements in oxidative stress [Peters et al. 2006], endothelial dependent flow-mediated dilation, enhanced bioavailability of nitric oxide; and transient changes in TPR may also be involved with extended training [Badrov et al. 2013; Baross et al. 2012; McGowan et al. 2006; McGowan et al. 2007; Peters et al., 2006].

A component of this dissertation involved the examination of several vasoactive (VEGF) and inflammatory biomarkers (interleukin-6; TNF-alpha) with known activity during and following exercise bouts with affects on blood vessel function and inflammation. Secondarily in this study we addressed confounding arguments on the importance of muscle mass and reductions in RBP by comparing two separate muscle groups bilateral bicep curl (IBC) and double leg extension (ILE), but at a similar intensity (15%MVC). This investigation incorporated a modified IET protocol (6, 2-minute contractions, separated by one minute of rest, three days/ week) for six weeks as RBP reductions have been observed as early as 4 weeks [Badrov et al. 2013a ; Wiley et al. 1992;]. A growing body of literature [Brook et al. 2013; Carlson et al. 2014; Cornelissen and Smart, 2013; Goessler et al. 2018; Kelley and Kelley, 2010; Lawrence et al., 2014;

Millar et al., 2014; Owen, et al. 2010; see Chapter 2-5] on the effectiveness of IET at reducing blood pressure exists, however this study was first to approach the field in this way. These data were evaluated with the intent to elucidate upon unknown mechanisms with regard to training adaptations to physical exercise. This study identified if factors found in blood following isometric contractions, provide an opportunity to characterize influences of IET induced reductions in RBP.

In this dissertation vasoactive (VEGF) and inflammatory biomarkers (IL-6 and TNF-α) we measured were not significantly altered following a single session of isometric exercise or over the course of a 6-week training period using two different muscle groups. Results of this dissertation show that reductions in RBP did not align with systemic biomarkers as initially proposed and BP adaptations may be occurring through an alternative mechanism or may be activated following a different stimulus. It is also possible that based on the results of this study, proposed factors may not be involved at all. Importantly, this is the first study to evaluate these select blood factors.

The findings of this dissertation add to the increasing body of research that is attempting to understand how IET effectively lowers blood pressure. While these data from Chapter 5 did not positively identify significant changes to proposed blood factors following an acute or training regimen of IET the author proposes the health of our participants, the exercise type, intensity, or duration may not have been significant enough to elicit responses. However, reductions in blood pressure using simple handgrip dynamometers in normotensive to hypertensive participants are well known, which would contradict the likelihood that larger muscle mass, or a greater intensity is required and that these markers are working through the proposed exercise adaptation.

New intervention strategies similar to IET may be involved. Short bouts of reduced blood flow by applying a tourniquet or cuff alone, cuff application + low intensity resistance exercise, or sustained muscle contraction (isometric) may promote an up-regulation in the activity of vasoactive pathways as well influence inflammation systemically. Modalities include blood flow restriction (BFR) training, remote ischemic conditioning (RIC), and physiological ischemic training (PIT) [Hess et al. 2015; Larkin et al. 2012; Ni et al. 2015; Shimizu et al. 2009; Shimizu et al. 2016; Takarada et al. 2000]. . IET is a surrogate intervention strategy combining blood flow restriction via muscle contraction and the effects of remote or physiological ischemia training by the production and activation of endogenous mechanisms for a combined effect following IET. However, this remains to be explored in greater detail. This dissertation provides a foundation in which future studies can build upon. In review of the literature and associated pathways, incorporating restriction of blood flow followed by subsequent reperfusion of tissue stimulates signaling pathways via secreted diffusible factors, lowering blood pressure and initiating protection in distal tissues [Gao et al. 2011; Hess et al. 2016a; Jones et al. 2014; Konstantinov et al. 2004; Loukogeorgakis et al. 2005; Madias, 2011, 2014, 2015; Ni et al 2017]. Next steps include investigation of alternative markers or modifications to the existing protocol with respect to intensity and exercise type and timing of blood draws. Based on the knowledge obtained in this dissertation and in review of the literature, lactate, VEGF, growth hormone (GH), hypoxia inducible factor one alpha (HIF-1a), IL-6 and TNF-a, VEGF mRNA, VEGF receptor FLT-1, angiopoietin and its receptor Tie-2, and NO metabolites (nitrite and nitrate) may be involved. This list alone provides enough evidence for future studies as these factors have also been altered following PIT, RIC, aerobic and resistance exercise [[Ameln et al. 2005; Gavin et al. 2004, 2007; Gustaffson et al. 2005; Kraus et al. 2004; Kraus et al. 2004; Lin et al. 2014; Nemet et al. 2002; Ross et al. 2013; Ryan et al. 2006; Rullman et al. 2007; Shimizu et al. 2016; Takarada et al. 2000; Trennery et al. 2007].

Resistance exercise is reported to incur significant changes in circulating plasma VEGF as well as upregulated VEGF mRNA immediately [Gavin et al. 2007] after exercise and remained elevated up through 24 hrs. post exercise [Ross et al. 2013]. Release of VEGF from muscle into circulation varies dependent on exercise modality, duration, and intensity [Ribeiro et al. 2017]. Gavin et al. [2007] assessed both acute and training responses in plasma and serum VEGF protein, along with VEGF receptor Flt-1 pre and post exercise that were all elevated at 0, 2 and 4 hrs. post exercise. Notably, there was an increasing trend but were no significant differences between 1-2 hours. A second study by Ross et al. [2013] observed a significant increase in VEGF following a single session of resistance exercise comprised of 15 repetitions of 6 different exercises incorporating arm (e.g. triceps pushdown) and leg (knee extension) muscle groups. A robust increase in VEGF was observed within 10-min of exercise cessation and remained elevated at both 2 and 24 hours post exercise. Duration of the exercise program (~12-minutes) by Ross et al. [2013] is similar to the present studies, however researchers utilized 3 circuits of 15 repetitions maximum using both arm and leg exercises. Similarly, a more recent publication determined a dose-response relationship, where higher exercise intensity promoted the highest angiogenic factors (VEGF, HIF-1a, and erythropoietin) post exercise [Ribeiro et al. 2017]. This study investigated the effects of a single bout of resistance exercise at three different intensities (60,70 or 80%) and was comprised of 3 sets of 12 repetitions with 4 exercises incorporating both upper and lower body musculature: bench press, dumbbell curl, dumbbell squat, and upright dumbbell row. Blood samples were collected at rest, post exercise immediately, 6 hours, and 24 hours post exercise with largest changes observed at 6 hours after exercise at 80% 1 repetition maximum. From these data and others, biomarkers that play a considerable role in the angiogenic cascade appear to be tied to both intensity and exercise type (both upper and lower body exercises).

With regard to the inflammatory cascade and plasma cytokines, BFR has also been associated with increased levels of IL-6 after exercise [Patterson et al. 2013; Takarada et al. 2000]. However, current data on IL-6 and TNF-a in response to low load resistance modalities are conflicting as several researchers observed no changes in these inflammatory cytokines similarly with data from the present investigation [Cezar et al. 2016; Rojas-Vega et al. 2010].

As previously described, alternative modalities more in line with isometric exercise training, like BFR [Larkin et al. 2012; Shimizu et al. 2016; Patterson et al. 2013, Takano et al. 2005;], RIC [Jones et al. 2014;Ueno et al. 2016] and PIT [Lin et al. 2014; Ni et al. 2016; Shen et al. 2009] have elicited significant pre -post changes in VEGF and VEGF mRNA. In contrast and also aligning with data produced in this dissertation, Rojas-Vega et al. [2010] did not observe significant changes in VEGF following a single bout of max effort knee extension exercise. Our subjects were recreationally active males engaged in some form of physical activity. Training status is likely an important variable in adaptations. Changes in VEGF and VEGF mRNA following PIT and RIC were observed in models of existing ischemia or induced ischemia by ligation was [Lin et al. 2014; Ni et al. 2017; Sandri et al. 2011; Shen et al. 2009]. Future work should continue to investigate the relationships between IET and vasoactive and inflammatory biomarkers as the present data is not yet enough to draw firm conclusions on these effects.

Limitations

The author and others performed all procedures regarding IET from the Laboratory of Systems Physiology successfully in the preceding studies. Members of the laboratory and others had conducted experimental procedures (analysis of blood biomarkers) RBP, and statistical evaluations of human participants previously. Over the course of each study the author expected minor difficulties with each subsequent investigation identifying pitfalls and limitations that occurred throughout. Additional limitations are provided discussed respective to each chapter above.

1. Adequate subject recruitment was difficult in investigations involving off campus sites and hospital environments. Furthermore, population dynamics (health status) have exacerbated complications relative to recruitment due to lack of interest, skepticism, and lack of compensation for longer training studies may have contributed to these complications.

2. Baseline RBP has been highly heterogeneous throughout each study. Moreover in studies 1-3 reductions in BP in the control group were unexpected, thus making analysis of the true effects of IET more difficult. The author suggests for all future investigations a longer pre-training period be used to establish true resting measurements. While more strict parameters may be used for specific populations of interest, this is

restrictive of what the goal of IET may be (e.g. community engagement) and could be an inherent limitation. Moreover, despite a randomization of participants in each study, the control group presented with a lower average group BP at baseline compared to groups completing IET. Therefore the true effects of IET (i.e. reductions in BP) may have been masked by significant differences between groups despite reductions in RBP between 6 and 13 mmHg that accompanied exercise training.

3. The final study was an exploratory investigation, and was the first of its kind. Data obtained provided valuable insight for future work exploring the presence or absence of biomarkers to establish cause and effect for adaptations to IET. Based on the study design used in study 4, reductions in RBP occurred but independent of systemic blood markers following IET. At this time these data may not be representative of adaptations to training in the current context.

4. The sample size of each investigation was relatively small. A larger number of participants with consideration for each study question is now required to confirm the results presented in this dissertation.

Future Directions

It has been established that the primary outcome measure of IET has been RBP. In the last 20 years the majority if not most of the IET research has reported significant reductions in RBP with training in normotensive [[Badrov et al. 2013; Devereux et al. 2010; Gill et al. 2015; Howden et al. 2002; McGowan et al. 2007; Ray and Carassco, 2000; Wiles et al. 2010; Wiles et al. 2017; see chapter 5] hypertensive [Badrov et al. 2013, Baross et al. 2012; See chapter 2,3 and 4], and medicated hypertensive [Badrov et al. 2013; McGowan et al. 2006; Milar et al. 2007; Millar et al. 2013; see Chapter 3] males and females within a broad age range utilizing several modalities of exercise [Lawrence et al. 2014; Millar et al. 2014]. Exercise modes include bilateral leg IET [Devereux et al. 2010; Gill et al. 2015; Howden, et al. 2002; see chapter 5] unilateral/ bilateral isometric handgrip [Badrov et al. 2013a, b; Badrov et al. 2016; Goessler et al. 2018; Wiley et al. 1992; McGowan et al. 2006; McGowan et al. 2007a,b; Millar et al. 2008; Taylor et al. 2003; See chapter 2,3, and 4] and bilateral arm curl [Howden et al. 2002; see chapter 5]. With a growing body of literature, IET can be implemented effectively using several avenues for successful HTN control both in the lab and in the community.

This dissertation successfully explored important demographics and study design factors that enhance, mitigate or may have no effect on reductions in RBP following IET. Further examination of the differences between subjects that experience decreases in RBP following IET and those who do not is important for future studies. Moreover, as discussed previously in section 6.2 State of the IET research, an analysis using individual participant data will likely provide the necessary detail to establishing a reference range or scale for implementing IET more effectively outside the laboratory.

For the first time our results would infer a training effect that is both multifactorial and phasic [Lawrence et al. 2014; Millar et al. 2014] following an extended detraining period. However the data was not representative of modifications within the resistance vasculature, evidenced by the lack of changes vasoactive and inflammatory biomarkers. Regardless of the present outcome future work should continue to explore systemic biomarkers as they have known influence over adaptations to aerobic and resistance training. Future studies should address the following;

- Performing individual patient data analyses to address associations between demographics, disease status, polypharmacy and success with IET.
- The American Heart Association deemed IET a Class IIB, level of evidence C for effectiveness. Therefore large-scale randomized trials to support its effectiveness to a wider audience (i.e. community-based studies) are required.
- Does volume of IET/ intensity of IET influence the production of proposed vasoactive factors whilst influencing inflammation similarly to other forms of exercise training?
- Does the active down regulation of proposed factors of importance attenuate responsiveness to IET interventions?
- Does over production or infusion of proposed factors accentuate responsiveness to IET?
- Are other vasoactive biomarkers more representative of responsiveness to IET?
- Does sexual dimorphism exist in the production of proposed factors and subsequent responsiveness or lack thereof with IET interventions?

Conclusions

This work identified the lasting effects of an extended isometric exercise training program (chapter 2), outlines the importance of disease and medications regimen in subject responsiveness to intervention (chapter 3), proposes the positive implications for home-based programming for training dissemination to the greater hypertensive population (chapter 4), and begins to elucidate upon unknown mechanisms contributing to lowered RBP with IET (chapter 5). This dissertation in its entirety addressed gaps in the literature regarding age, disease, length of participation, home-based effectiveness, and produced data for future work to explore mechanisms related to IET.

In conclusion this dissertation helped to disseminate critical next steps, providing an opportunity for effective programming, successful community integration, and elucidating on a potential mechanism contributing to BP reductions induced by IET. It is highly recommended that future work implement a multi-center community based strategy concomitant with blood sampling thus aiding in the fight against HBP both in the lab and in the community.

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APPENDIX 1: THOMAS R. REYNOLDS GRADUATE RESEARCH FELLOWSHIP

Application: The Thomas L. Reynolds Graduate Student Research Award

Tittle of Proposed Project: THE ROLE OF BLOOD MARKERS IN ISOMETRIC EXERCISE TRAINING INDUCED REDUCTIONS IN RESTING BLOOD PRESSURE

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Dissertation Advisor: Dr. Reuben Howden (Associate Professor of Kinesiology)

1. Problem Statement: High blood pressure is the leading global risk factor for mortality [1]. 72 million people in the United States are affected by high blood pressure; costing the healthcare system ~$46 billion dollars per year [Merai et al.2016, Mozzafarian et al. 2015]. Recommended lifestyle changes (diet and exercise) and prescription medications have not been universally successful at high blood pressure control.

Many studies have evaluated the capacity of exercise to lower blood pressure (BP). Isometric exercise training (IET) has been reported to lower BP significantly. During IET, muscles contract but no body movement occurs (e.g. handgrip). IET is simple, safe, and inexpensive, taking approximately 11 minutes per day, 3 days per week [9]. While IET has been shown to lower BP in many groups of people, little is known about the mechanisms (e.g. blood markers, muscle mass) that contribute [2]. Improved knowledge of mechanisms for IET-induced BP reductions is the first step to designing individualized IET protocols to maximize the efficacy of IET as a supplementary therapy for BP control.

2. Objective(s) and methodology of proposed project: This project will test the effects of a muscle mass dependent IET program (6-weeks of arm vs. leg exercise) on blood vessel controlling factors, markers of inflammation and reductions in BP. It is possible that IET influences blood vessel controlling and anti-inflammatory factors to modify blood vessel function and thus lower BP after several weeks of training [3]. This study is not only novel and innovative for the field, but is critically important in reducing the burden of high BP. OBJECTIVE: To establish a relationship between blood vessel controlling factors, vascular endothelial growth factor (VEGF) and hypoxia inducible factor 1 alpha (HIF-1a); as well as inflammatory factors interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-a), following IET in two muscle groups (arms vs. legs). These factors have been identified in previous investigations to play an important role in responses to similar forms of exercise [5, 6, 8] and blood pressure control [7]. However, these components have not been investigated in IET programs. This study will be conducted with Dr. Reuben Howden as my final project in the Interdisciplinary Biology PhD program.

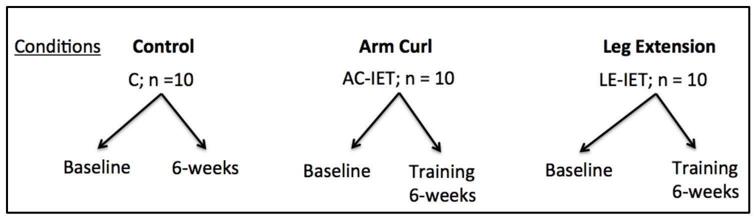

Figure 1: Overview of proposed experimental design. Using isometric exercise training in both limbs, double arm curl (AC) vs. double leg extension (LE), with control; blood markers and BP will be measured at baseline and 6 weeks of training. In exercise groups, IET at 20% maximal voluntary contraction will take place 3 days per week for 6-weeks.

METHODS: Study Design: Following an established protocol used in our lab, this study will be a randomized controlled trial with 3 groups, double arm curl (AC) exercise, double leg extension (LE) exercise, and control (*see figure 1*). Isometric Exercise Training Protocol: Participants will perform 2-minute isometric contractions at 20% of pre-determined maximum strength, followed by 1 minute of rest, repeated 6 times per session. Sessions will be repeated 3 days per week for 6 weeks. Participants: 30 College aged males (healthy non-smokers and not regular exercisers) will be asked to provide informed consent prior to participating in this study. Participants must possess no contraindication to performing the exercise prescribed. Blood Pressure and Heart Rate: Resting BP and heart rate will be measured 3 days per week for 6-weeks using an established protocol in our lab. Blood Collection & Analysis: An experienced phlebotomist will collect 6mL of blood from participants' arm vein using standard procedures at baseline and 6-weeks of training. Blood samples will be analyzed for the blood factors described above. The minimum calculated sample sizes for a power level of 0.80 and an alpha level of 0.05 is 10 subjects per group (SAS, Cary, NC). Sample sizes were calculated using anticipated effect sizes including expected BP and blood factor values. Expected Outcomes: 1) An analysis of blood vessel controlling factors (VEGF and HIF1-a) will be increased following IET, and will be highest in the LE group. Markers of inflammation (TNF-a and IL-6) will be decreased following training, and will be lowest in LE group. 2) Muscle mass used in IET will influence BP reductions and the release of blood factors described above. This project is an exploratory investigation and these results will provide necessary data allowing me to finish my dissertation and gather preliminary data for future extramural funding proposals.

3. Timeline for Project (estimated dates): This project has received approval from both the Institutional Review Board and Institutional Biosafety Committee and is set to begin during the first summer session of 2017. Data will be collected throughout the summer sessions. All data collection and analyses are set to be completed by end of December

2017. Following analysis, these data will be used to complete my dissertation work, as well as providing essential new information in the research field of IET as a supplementary BP management tool.

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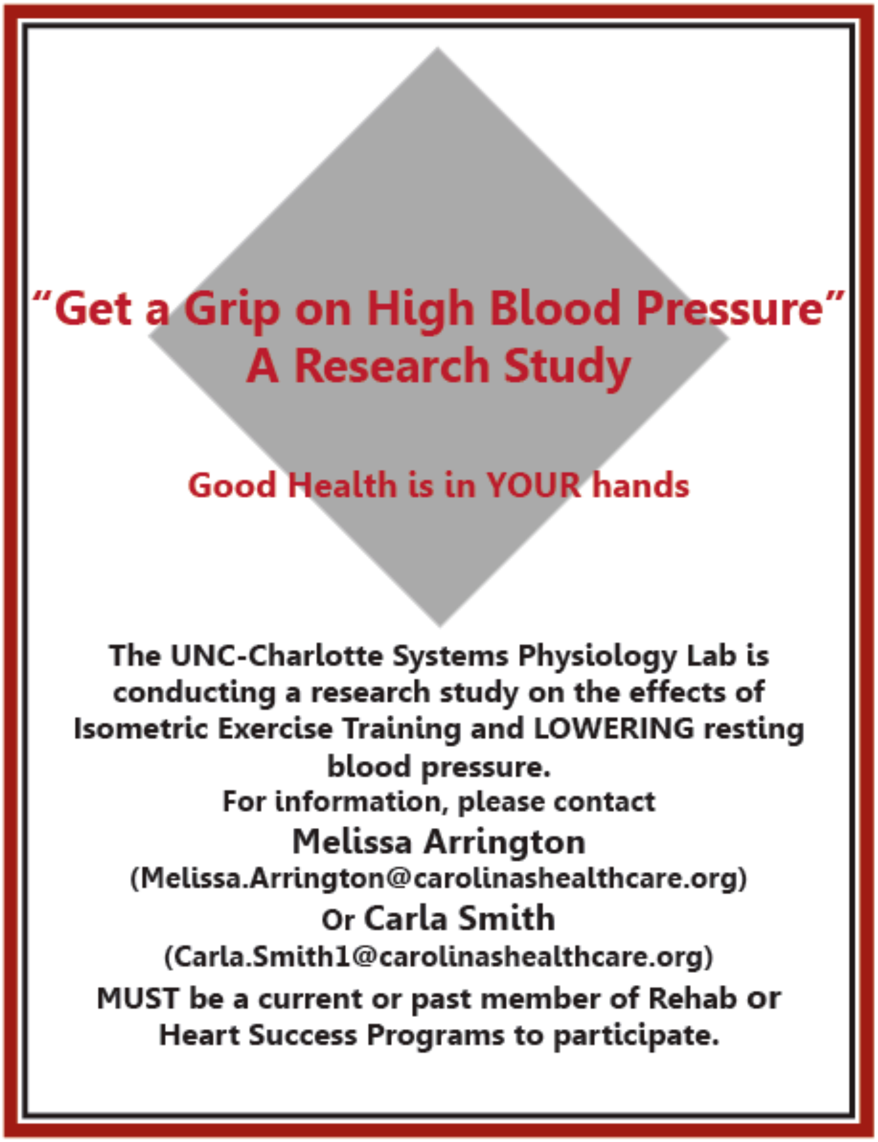
APPENDIX 2: STUDY 2. RECRUITMENT FLYER



APPENDIX 3: STUDY 3. PHONE RECRUITMENT SCREENING QUESTIONNIARE

"Hello, my name is __________________. I am calling for ***insert caller name here***.

"Hello, Ms. /Mr./ Miss/Mrs. ***caller name***. I am calling about the study on handgrip exercise and blood pressure being conducted at UNCC. Is this a good time to talk?"

"Can I tell you a little bit about the study?"

"This study will look at the effect of handgrip exercise training on resting blood pressure. As part of this study we will also ask you about other things you may do to manage your blood pressure such as taking medication, eating a healthy diet, watching your weight and so on. Handgrip exercise has been successful in lowering blood pressure in many groups of people.

For this study, you will use a handgrip device to exercise, which is similar to squeezing a stress ball.

For this study you will be put into one of three groups: a delayed treatment/ control group that does not perform the exercise (non-training group for 18 weeks; later given the option to complete the intervention of your choice) a group who participates in group based handgrip exercise, and a group who participates in home-based handgrip exercise. If you are eligible for the study, we will randomly assign you to one of the groups above. If you are placed into the delayed treatment/ control group you will be asked to follow your normal routine for 18-weeks but we will want you to come to campus so we can take your blood pressure and ask you some questions at 4 time points (week zero, 6, 12 and 18). After the 18 weeks are up, you can choose to do either version of the exercise program.

If you are in the Group Based exercise program you will exercise with a handgrip squeezing device that includes 4 squeezes of 2 minutes each at 30% of your maximal handgrip strength. Your participation will be for approximately 20 weeks. You will exercise 3 times per week for a total of 12 weeks in our lab in the Cameron building. Each exercise session lasts about 15-20 minutes. This will be followed by 6 weeks of no handgrip exercise.

If you are in the Home-Based exercise program you will exercise with a handgrip squeezing device that includes 4 squeezes of 2 minutes each at 30% of your maximal handgrip strength. Your participation will be for approximately 20 weeks. You will exercise 3 times per week for a total of 12 weeks, followed by 6 weeks of no group handgrip exercise. You will exercise at home following a YouTube/or DVD video. Regardless of what group you are in, each time you complete a data collection point, you will be entered into a drawing for a $100 gift card. This is a one in twenty chance of winning at each of 4 times.

We are looking for UNCC graduate students, or employees between the ages of 21-65 years old, who have high blood pressure, and who can perform handgrip exercise without extreme discomfort.
Are you still interested in the study?"

If yes, then: "I will now ask you several pre-screening questions to insure your eligibility in the study."

If no, "thank you very much for calling us."

Pre-Screening Measures

1. Are you between 21 and 65 years old? **Y / N**

2. Are you currently prescribed any blood pressure or heart-related medications? For example – statins, diuretics or "water pills," or any other pill your doctor has told you is for your heart or blood pressure. **Y / N**

    Has a doctor ever told you that you have high blood pressure?
    Y/N
    If "no" to #3. Is your blood pressure usually >130/80 and <160/100?
    Y/N [*If no, participants can come to the lab and have their BP checked*]
3. Do you have any physical limitations causing pain or discomfort when using your hands?

    Y / N
4. Do you know of any reason why you would not be able to read or understand the details of the study? **Y / N**

5. For women: Are you, or do you think that you might be, pregnant?

    Y / N

[If participants answer questions 1-2 with "yes" and 3-5 with "no"] - *Congratulations you are eligible for the study. We'd like to schedule you to come in for your blood pressure visit. I have some detailed instructions to give you for that.*

- *When you scheduled to have your blood pressure taken, we ask that you do the following:*
    - *Have nothing to eat or drink, except water, for 2 hours prior*
    - *No vigorous physical activity outside of your normal routine*
    - *No caffeine or alcohol for at least 12 hours before*
    - *Take all your medications at the prescribed time and dosage*

Do you have any questions for me now? Let's schedule your blood pressure visit then.

[If participant answers "No" to any of questions 1-3 or "yes" to 4 or 5, then…] *–I'm sorry you are not eligible for this study. We really appreciate your willingness to participate in research. Thank you so much.*

APPENDIX 4: STUDY 3. RECRUITMENT FLYER

Have you been told by your doctor that you have high blood pressure?

We are looking for people with high blood pressure to participate in a handgrip exercise study to reduce blood pressure. Each exercise session takes about 15 minutes.

If you have high blood pressure, are between ages 21-65, and work at UNC Charlotte or are a graduate student, you may be eligible.

This research study is approved by the Institutional Review Board at University of North Carolina Charlotte – approved 5/18/2015 and expires on 5/17/2016.

If you want to participate in this study, please contact:
uncc.IET@gmail.com

APPENDIX 5: STUDY 3. RECRUITMENT EMAIL FOR PROSPECTIVE PARTICIPANTS.

SUBJECT LINE: Research Study to Reduce High Blood Pressure

Drs. Jan Warren-Findlow and Reuben Howden are performing a study on the effects of isometric exercise training on lowering blood pressure. Isometric exercise is a form of strengthening exercise, in this case squeezing a handgrip device.

If you have high blood pressure and are in between the ages of 21 to 65, and you are faculty/staff employed by UNC Charlotte, or a graduate student at UNC Charlotte, you may be eligible for this research study.

You will be in one of 3 groups: a group who performs the handgrip exercise 3 days per week at the Laboratory of Systems Physiology at UNC Charlotte; a group who performs the handgrip exercise 3 days per week at home using a video; or the delayed treatment group who will not perform these exercises until later. The exercise portion of the study will last 12 weeks, followed by a 6 week follow up period. At the end of the 12 weeks, control group members will have the option of participating in either exercise program. We will also measure your blood pressure and ask you some health and lifestyle questions using a brief survey at 4 time periods during the study. Whichever group you are assigned to, you will be eligible to win a $100 gift card per group at each data collection point (baseline, 6 weeks, 12 weeks and 18 weeks).

If you are interested in participating, please contact us at uncc.IET@gmail.com. Thank you!

This study has been approved by the UNC Charlotte Office of Protection for Human Subjects (Protocol #15-04-13) for a period of one year.

APPENDIX 6. HOME-BASED IET PARTICIPANT PACKET

HOM IET Participant Packet - 2016-2018

Home Video YouTube Links for Participants

Thank you for participating in our study! Below you will find the links to the videos you will use to follow along with your home-based isometric exercise sessions.

1. Introductory Video- You MUST watch this video at least once before engaging in any isometric exercise sessions!! As you become comfortable with the IET process, you may not need to watch this video every time.

Video 1 Link: https://youtu.be/VeeRYQJBD8M

2. Exercise Session Video- Follow along with this video, which features an on- screen timer, *EVERY* time you complete an exercise session (3 times each week).

Video 2 Link: https://youtu.be/8wxeiVF2RX

Maximal Voluntary Contraction (MVC)	30% Exercise Load (kg)	Maximal Voluntary Contraction (MVC)	30% Exercise Load (kg)
1	0.3	40	12
2	0.6	41	12.3
3	0.9	42	12.6
4	1.2	43	12.9
5	1.5	44	13.2
6	1.8	45	13.5
7	2.1	46	13.8
8	2.4	47	14.1
9	2.7	48	14.4
10	3	49	14.7
11	3.3	50	15
12	3.6	51	15.3
13	3.9	52	15.6
14	4.2	53	15.9
15	4.5	54	16.2
16	4.8	55	16.5
17	5.1	56	16.8
18	5.4	57	17.1
19	5.7	58	17.4
20	6	59	17.7
21	6.3	60	18
22	6.6	61	18.3
23	6.9	62	18.6
24	7.2	63	18.9
25	7.5	64	19.2
26	7.8	65	19.5
27	8.1	66	19.8
28	8.4	67	20.1
29	8.7	68	20.4
30	9	69	20.7
31	9.3	70	21
32	9.6	71	21.3
33	9.9	72	21.6
34	10.2	73	21.9
35	10.5	74	22.2
36	10.8	75	22.5
37	11.1	76	22.8
38	11.4	77	23.1
39	11.7	78	23.4

Written Instructions for Participants: HOM IET

As a participant in this project you will be participating in isometric handgrip exercise. This is type of training is known to have the potential of lowering your resting blood pressure in as little as 4 weeks. We want you to stick with this 11-minute session diligently and consistently 3 days per week for the next 12 weeks. This exercise program may have significant affects on your overall health, with the goal of lowering your resting blood pressure. To begin, please follow the protocol outlined below.

GETTING STARTED

1. GET HANDGRIP: Remove the handgrip from the box. This is a handgrip dynamometer. It allows us to measure your handgrip strength.
2. ADJUST HANDGRIP: Take your handgrip device and as you grip the device make sure it sits comfortably under the second knuckle in your dominant hand. If you need to adjust the device for a better fit, twist the small silver/gray knob in the middle of the handgrip to raise and lower the grip. Once you have the sizing right, you should rest the handgrip device in your lap with the screen facing up.
3. GET MATERIALS: Inside your box you will find a participant log. Please get something to write with and write today's date on the appropriate page of the log. You will also find, a chart, called the MVC chart and a recording log. The MVC chart helps to determine your exercise load for every day that you complete the handgrip exercise session.

DETERMINE MAXIMAL VOLUNTARY CONTRACTION

At the beginning of every session, the first thing you need to do is figure out how hard you are going to squeeze the grip device during that day's exercise session. You will do 3 handgrip squeezes, each time squeezing as hard as you can. You will use the largest of those 3 numbers to determine your exercise load. We call this a maximal voluntary contraction (MVC), or in other words the strongest you can squeeze in 1-2 seconds with your dominant hand. So if you are right-handed, that's your right hand and if left-handed, use your left hand. You will complete this protocol at the beginning of each exercise session.

1. TURN IT ON: Turn your device on by pressing the ON/SET button. Once the device is on, press the START button. The screen should read 0.0 kg. If your device says 0.0 lbs., click the ON/SET button once until the screen reads kg.
2. PREPARE TO SQUEEZE: Sit upright with your feet flat on the floor resting the handgrip device in your lap. When you're ready, squeeze as hard as you can for 1-2 seconds. GO!
3. MVC CHART: Look for the number displayed at the top of your device on the MVC chart and find the corresponding 30% exercise load. To read this chart,

look down the first column, as these numbers represent your strongest squeeze value. Next read directly across from that value to find the corresponding 30% load that matches with that number. For example, if you squeeze 20.5kg (found in the left column) your exercise load for the session will be approximately 6.5kg (found in the right column). Now the first MVC column only goes up to 39kg. If your MVC is greater than 39kg look over to the third column in the chart for numbers 40-78kg and look for the corresponding 30% load just as before.

4. RECORD MVC IN LOG: Record your MVC for the day in your exercise log. It is important both for you and for us to know how you are doing and the log will help with that.
5. REPEAT: Repeat steps 1-4 two more times, for a total of THREE MVC's. Squeeze will be recorded in the box labeled MVC 1; squeeze 2 will be recorded in the box labeled MVC 2; and so on.
6. SELECT THE HIGHEST, FIND 30%, AND RECORD: Look at your three numbers and pick the highest of the three. For all measures of MVC that end in .5 and above round up, and .4 and below you will round down to the next whole number. Now look at the 30% MVC chart. Using your highest squeeze number, look down the first column to find your number. Then read directly across the chart to find the corresponding 30% load that matches with that number. For example, if you squeeze 20.5kg, you round up to 21kg, and look for the exercise load that corresponds with 21kg. Your exercise load for the session would be approximately 6.3kg. Record this number, your exercise load, on your log next to the first 3 numbers.
7. REST: Take a few minutes to rest your hand.

<u>BEGIN EXERCISE SESSION!</u>

Now that you know your exercise load for today, you are ready to exercise. This session will consist of four 2-minute handgrip squeezes using the exercise workload you just determined using the MVC chart. After each 2-min handgrip squeeze you will have 1 minute to rest. To help you keep track of time, you can follow along with the clock on screen of your video, or you can follow along with your instructor if you are in class.

As you squeeze, the number on your handgrip screen will likely fluctuate. Do your best to keep it as close as possible to your exercise workload mark. It may not be perfect but as close as you can is what we're looking for.

This type of exercise may be slightly uncomfortable and your hand may get tired; that feeling is normal. However should you feel pain at any time, STOP the exercise and call us right away.

1. DATE: Be sure today's date is written in your participant log.
2. TURN IT ON: Turn your device on by pressing the ON/SET button. Once the

device is on, press the START button. The screen should read 0.0 kg. If your device says 0.0 lbs., click the ON/SET button once until the screen reads kg.

3. PREPARE TO SQUEEZE: Sit upright with your feet flat on the floor resting the handgrip device in your lap. Check your MVC number- this is the number you will try to stay at when you are doing your 2-minute squeezes.
4. SQUEEZE 1: When you're ready, begin squeezing. GO! Try to hold the squeeze to that your handgrip stays as close as you can keep it to the MVC number you determined. This is hard! Hold for 2 minutes… and…
5. STOP- REST 1: Please rest for one minute.
6. REPEAT: Repeat steps 2-5 three more times for a total of FOUR SQUEEZES.

APPENDIX 7: STUDY 4. RECRUITMENT EMAIL FOR PROSPECTIVE PARTICIPANTS

The subject line of the message is: Research Study to Investigate the Effects of Muscle Mass and Blood Markers Released After Exercise

Email text:

Biology and Kinesiology graduate student Ben Gordon along with Drs. Reuben Howden, Joe Marino, and Jeanette Bennett are performing a study on the effects of isometric exercise training, muscle mass, and secreted blood markers. Results of this study have the potential to help reduce the negative impacts of poor blood pressure management, and improve your overall health.

If you are an identifying male, at least 18 years of age, and you are a student at UNC Charlotte, you may be eligible for this research study. Participants who complete study requirements will be given a $75 gift card for their participation.

If you are interested in participating, please contact us at bgordo18@uncc.edu to schedule a resting blood pressure screening and to complete a short questionnaire to determine your eligibility for the study.

Thank you for your time and we look forward to your participation.

Sincerely,
Ben Gordon and the Research Team
This study has been approved by the UNC Charlotte Office of Protection for Human Subjects (Protocol #16-0087) for a period of one year (12-20-17).

APPENDIX 8: STUDY 4. RECRUITMENT SCREENING QUESTIONNAIRE

Male UNC-Charlotte Graduate or Undergraduate Student	Yes	No
Blood Pressure >90/ 60 but <130/81 mmHg	Yes	No
18 years old	Yes	No
Physical Limitations causing pain/ discomfort during maximal double leg or double bicep curl isometric contractions	Yes	No
English speaking	Yes	No
Prescription or over-the-counter medications that influence cardiovascular activity, have mood altering or anti-inflammatory effects	Yes	No
Current smoker or quit less than 6 months ago, smokless tobacoo, marijunana, e-cigs, hookah, cigars Use of illicit drugs like heroin, cocaine, methamphetamine, ecstasy, LSD, hallucinogens or their derivatives or abused prescription drugs in the past 12 months.	Yes	No
Acute infection or illness	Yes	No
Current use of high dose anti-inflammatory medications (>800 mg/day Ibuprofen or >1250-1375mg/ day Naproxen) like advil or aleve, or steroids continuously for up to 10 days.	Yes	No
Diagnosis of history of chronic disease (i.e., hypertension, congenital heart disease or disorders, cardiovascular disease such as heart attack or stroke)	Yes	No
(i.e., asthma, diabetes, obesity, autoimmune disorders, cancer, major depression, cardiovascular disease, celiac's disease);	Yes	No
Surgery in the past 3 months	Yes	No
Ability to read and understand the informed consent	Yes	No