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The Importance of Modality as a Determinant of the Antihypertensive Effects of Exercise

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Aerobic exercise reduces blood pressure (BP) among those with hypertension, while limited evidence suggests similar BP benefits may result from isometric handgrip (IHG) resistance exercise. Exercise-induced reductions in arterial stiffness may partially explain the BP lowering effects of exercise; however, evidence is mixed. We compared the BP and arterial stiffness responses to acute and chronic aerobic versus IHG exercise in the same group of people, and also examined if these responses were correlated. Overweight adults with prehypertension (n=27) randomly completed three experiments: aerobic [60% peak oxygen uptake (VO_2peak), 30 minutes]; IHG [30% maximum voluntary contraction (MVC), 4x2 minutes bilateral]; and non-exercise control. We measured carotid-femoral pulse wave velocity (PWV) by applanation tonometry before and after each experiment. Subjects left the laboratory wearing an ambulatory BP monitor. Systolic and diastolic BP (SBP/DBP) were lower after aerobic versus IHG (5.2±1.7/3.5±1.3mmHg, p=0.01) and control (6.8±1.9/5.4±1.4mmHg, p=0.001) over the awake hours, with no difference between IHG versus control (p>0.05). A subset of participants then randomly completed either eight weeks of aerobic (n=6, 60% VO_2peak, 45 min•day^{-1}) or IHG (n=5, 30% MVC, 4x2 minutes bilateral) training. Awake SBP was lower after versus before aerobic training (7.6±2.0 mmHg, p=0.02), while sleep DBP was higher after IHG training (7.5±1.8 mmHg, p=0.03). PWV responses to acute and chronic exercise did not differ by modality or

correlate with BP responses ($p>0.05$). Our findings indicate that aerobic exercise is superior to IHG as antihypertensive therapy and should continue to be recommended for its immediate and sustained BP benefits.

Keywords: Acute, Aerobic, Ambulatory Blood Pressure, Arterial Stiffness, Hypertension, Isometric Handgrip, Lifestyle Therapy, Prehypertension, Postexercise Hypotension, Resistance, Training

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Chapter 1 - Introduction

Background and Significance

High Blood Pressure is a Major Public Health Problem

Hypertension [systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg] is a major public health issue affecting ~1 billion (17%) adults globally[1] including ~80 million Americans (33%)[2], a percent that has stabilized over the last 15 years[3]. Hypertension is a major risk factor for coronary heart disease, stroke, congestive heart failure, chronic kidney disease, and peripheral arterial disease, and decreases life expectancy by an average of five years[2]. Hypertension incurs $130.7 billion direct medical costs and $25.4 billion indirect costs due to lost productivity annually in the United States[1]. These direct and indirect costs are expected to double by 2030[1].

Furthermore 68 million (30%) American adults have prehypertension (SBP ≥120 to <140 mmHg and/or DBP ≥80 to <90 mmHg)[2]. Prehypertension progresses rapidly to hypertension for one in five people with prehypertension will develop hypertension within four years[4]. Those with prehypertension at age ≤50 years have double the lifetime risk of stroke, heart failure, coronary heart disease, and intermittent claudication compared to those with normal BP at the same age[5]. Nearly all Americans will eventually develop hypertension if they live long enough[2]. Therefore, the Eighth Joint National Committee and the American Heart Association (AHA)/American College of Cardiology 2013 Lifestyle Work Group recommend lifestyle modifications to prevent, treat, and control hypertension[6, 7], including the Dietary Approaches to Stop Hypertension eating plan, reduced dietary sodium and alcohol intake, and regular aerobic physical activity.

The Antihypertensive Effects of Aerobic Exercise

The American College of Sports Medicine (ACSM) position stand on exercise and hypertension concluded aerobic exercise training (i.e., chronic exercise) reduces BP 1 to 3 mmHg among individuals with normal BP and 5 to 7 mmHg among those with hypertension[8]. These BP reductions lower cardiovascular disease risk by 20 to 30% among those with hypertension[4]. We and others have shown that aerobic exercise also acutely reduces BP anywhere from 2 to 20 mmHg among adults with hypertension after a single exercise session for up to 22 hours[9-15]. This short-term BP response to exercise is termed *postexercise hypotension* (PEH).

A growing literature indicates the antihypertensive effects of aerobic exercise training (i.e., chronic or long-term) are related to the acute effect or PEH, suggesting PEH may be an important clinical characteristic that can be used to predict the BP response to more long-term exercise training. Two recent studies[16, 17] have found PEH correlates strongly with the BP response to exercise training, accounting for up to 85% of the SBP and 56% of the DBP response to exercise training. Thus, when investigating the BP benefits of exercise, the BP response to acute exercise cannot be isolated from the response to more long-term exercise training. These acute and chronic antihypertensive effects of aerobic exercise form the basis of the ACSM recommendations that adults with high BP perform 30 to 60 minutes per day of continuous or accumulated moderate intensity (40% to 60% peak oxygen consumption, VO_{2peak}), aerobic exercise on most days of the week supplemented by two to three days per week of moderate intensity (60% to 80% one repetition maximum), dynamic resistance training to lower BP[8].

Unfortunately, 162 million American adults (54%) do not engage in the recommended amount of aerobic exercise to lower BP[18]. Reasons for the lack of adherence to aerobic exercise may include boredom[19], cost[19], accessibility[19], and injury or disability[20, 21]. Therefore it is worthwhile to explore whether there exists an alternative exercise modality which is less time intensive, less expensive, more accessible, and less likely to cause musculoskeletal problems than aerobic exercise and as or more effective at reducing BP among those with high BP. Such an alternative modality could improve the efficacy of exercise as lifestyle therapy to prevent, treat, and control hypertension.

The Antihypertensive Effects of Isometric Handgrip Resistance Exercise

Recent evidence suggests that isometric handgrip (IHG) resistance exercise may be an attractive, affordable, and accessible exercise modality for people with high BP[22]. For, several randomized controlled trials have indicated that the BP reductions that result from acute (i.e., PEH)[23] and chronic (i.e., training)[24-28] IHG resistance exercise appear to be equal to or even greater than those that result from aerobic exercise. Millar et al[23] reported an acute IHG session consisting of four, two minute low intensity (30% maximum voluntary contraction, MVC), hand contractions to total eight minutes of IHG reduced BP 4 to 5 mmHg over 30 minutes in the laboratory among older men with normal BP. In addition, five studies[24-28] reported eight to ten weeks of IHG training for three days per week reduced BP 3 to 15 mmHg among young[26, 28] and older[24, 25, 27] adults with normal[24, 28] and high BP[25-27].

In contrast, Olher et al[29] reported that BP was not different after versus before acute IHG resistance exercise over 60 minutes in the laboratory among older women

with high BP. In agreement with Olher et al[29], Stiller-Moldovan et al[30] reported that ambulatory BP measured for 24 hours under conditions of daily living was not different after than before eight weeks of IHG training among older men and women with high BP. Given this limited and mixed literature on the BP lowering effects of IHG resistance exercise, the AHA cautioned more data are needed to establish the efficacy and safety of IHG resistance exercise as antihypertensive therapy[22].

The first limitation of the existing literature is that Millar et al[23] and Olher et al[29] measured PEH following acute IHG exercise for 60 minutes in the laboratory, so that the duration of PEH following acute IHG exercise under conditions of daily living should it occur is not known[23, 29]. Second, no study has yet been done that has compared the magnitude and duration of PEH following IHG resistance versus aerobic exercise among the same individuals with high BP. Third, the majority of the above studies included older adults (55 to 80 years)[24, 25, 27, 31] with established hypertension treated with antihypertensive medication[25, 27, 31], while just one previous study included young adults (20 to 52 years) with prehypertension[26]. Prehypertension at a young age represents a crucial period of therapeutic intervention to prevent and delay the progression to hypertension[2, 4]. Therefore, the narrow scope of populations evaluated for the BP response to IHG limits the generalizability of the existing literature. Nonetheless, the clinically significant reductions in BP observed in the above studies[23-28, 31] suggest that IHG could be effective antihypertensive therapy if further studies can address these limitations. Therefore, a study directly comparing the acute and chronic antihypertensive effects of IHG, aerobic exercise, and non-exercise control within the same group of adults in the early stages of hypertension both at rest and under

ambulatory conditions of daily living is warranted.

The Influence of Aerobic and Isometric Handgrip Resistance Exercise on Central Arterial Stiffness

Elevated central arterial stiffness is an independent cardiovascular disease risk factor[32-35]. Central arterial stiffness is also implicated in the etiology of hypertension[36, 37]. Two community-based studies reported that carotid-femoral pulse wave velocity (PWV), an indicator of central arterial stiffness, directly associated with risk of developing hypertension among men and women with normal BP (n=449 and 1,759 respectively) over a follow-up period of 2 to 12 years[36, 37].

Some evidence suggests that acute and chronic aerobic exercise may reduce central arterial stiffness. Kingwell et al[38] found central arterial stiffness was lower than baseline immediately following 30 minutes of moderate intensity acute aerobic exercise among healthy adults with normal BP. On the other hand, three other studies found central arterial stiffness was not different than baseline following 30 minutes of moderate intensity, acute aerobic exercise among adults with high BP[39-41].

In addition, Huang et al[42] meta-analyzed the influence of aerobic exercise training on central arterial stiffness among 610 young to older men and women (20 to 70 years) who were overweight to obese [body mass index 26.1 to 34.9 $kg*m^{-2}$] with pre- to stage 1 hypertension (SBP 121 to 150 mmHg / DBP 75 to 85 mmHg). Huang et al[42] included 15 trials (*n*=325 assigned to exercise training; *n*=285 to non-exercise control) with diverse aerobic training programs, including cycling, walking, running, and swimming. Aerobic exercise was performed three to five days per week at moderate to vigorous intensity (40% to 75% VO_{2peak}), 30 to 60 minutes per day, for eight to 26

weeks[39, 43-58]. On average, central arterial stiffness decreased following aerobic exercise training by 0.88 meters per second [95% CI (-1.37, -0.88), p<0.01][42].

However this mean difference exhibited high heterogeneity (I^2= 91%, p<0.01)[42], which Huang et al sought to explain through moderator analysis and identified several subgroups of interest. Specifically, arterial stiffness was reduced to greater levels when patients performed aerobic exercise training for a greater number of weeks [four to eight weeks, -0.35 meters per second (-0.68, -0.02); nine to 16 weeks, -0.69 meters per second (-1.13, -0.25); 16 to 26 weeks, -1.19 meters per second (-1.92, -0.47)] and/or achieved greater improvements in VO_{2peak} [≤10% improvement in VO_{2peak}, -0.40 meters per second (-0.52, -0.28); 10% to 15%, -0.95 meters per second (-1.29, -0.61); 15% to 20%, -1.41 meters per second (-3.06, 0.25); >20%, -1.72 meters per second (-2.39, -1.04)]. The results from Huang et al[42] provide evidence that aerobic exercise may be effective in lowering central arterial stiffness among adults with high BP, but their findings are limited by a small sample of studies (k=15) with heterogeneous outcomes depending upon the length of the exercise program and changes achieved in physical fitness.

Mixed evidence suggests changes in central arterial stiffness following aerobic exercise may be a mechanism contributing to the antihypertensive effects of acute and chronic aerobic exercise. Specifically, an earlier meta-analysis of the influence of aerobic exercise training on arterial stiffness among men and women with high BP by Montero et al[59] assessed the correlation of changes in arterial stiffness and SBP. Similar to the later meta-analysis by Huang et al[42], the cohort captured by Montero et al[59] (k=14 trials including n=472 subjects) were middle aged to older men and women

with overweight to obesity and pre- to stage 1 hypertension. Also similar to the later meta-analysis[42], the cohort captured by Montero et al[59] performed aerobic exercise of various types three to six days per week at moderate to vigorous intensity, for 30 to 60 minutes per day over four to 26 weeks. Montero et al[59] reported that arterial stiffness was significantly reduced [d_+= -0.38 (-0.74, -0.01); p=0.04; k=7) among samples that lowered resting SBP to levels greater than the median value (< -7.6 mmHg). Meanwhile, samples that reduced resting SBP by ≥ -7.6 mmHg did not reduce arterial stiffness following aerobic exercise training [d_+= -0.04 (-0.27, 0.19); p=0.76; k=7]. In support of these findings, other investigators have found reductions in central arterial stiffness following moderate intensity aerobic exercise training concurrent with BP reductions among adults with high BP[39, 44, 45, 57].

In contrast, others have found that BP changes following acute[38] and chronic[60] aerobic exercise occurred independently of central arterial stiffness changes. In addition, no individual studies have reported whether the change in central arterial stiffness and BP following exercise were correlated between subjects. Furthermore, the association of elevated central arterial stiffness with future development of hypertension[36, 37] implies that elevated central arterial stiffness may cause the development of hypertension; however, it is also possible that hypertension causes the development of elevated central arterial stiffness[61]. Indeed, increased pressure pulsatility as occurs in hypertension degrades arterial elastin and increases stress on arterial collagen, responses which elevate central arterial stiffness[62-66]. Finally, acute aerobic exercise[39-41] and relatively short aerobic exercise training programs (i.e., four to eight weeks)[42] achieving small changes in physical fitness (i.e., VO_{2peak} improvement

≤10%)[42] appear less effective at reducing central arterial stiffness, compared to longer aerobic exercise training programs (i.e., 16 to 26 weeks)[42] achieving greater changes in physical fitness (i.e., VO_{2peak} improvement >20%)[42]. Thus, further study is required to resolve whether acute and chronic aerobic exercise influence central arterial stiffness, whether such changes are correlated, and whether such correlation suggests central arterial stiffness reductions may partially account for the antihypertensive effects of aerobic exercise.

No studies to our knowledge have measured central arterial stiffness following acute or chronic IHG. However, among adults with high BP acute IHG reduced sympathetic nerve activity[23, 67] and oxidative stress[68]. Furthermore IHG training also reduced sympathetic nerve activity[25, 31] and oxidative stress[68] as well as endothelium-mediated vasodilation[69]. As these responses reduce central arterial stiffness[70-73], IHG may also reduce central arterial stiffness. Moreover, these reductions in central arterial stiffness may be a mechanism partially explaining the acute and chronic antihypertensive effects of IHG.

Purpose of Study

The purpose of this study was to compare the BP and arterial stiffness responses to acute and chronic aerobic and IHG resistance exercise among adults with high BP, and examine if changes in arterial stiffness account for some of the variability in the BP response following acute and chronic aerobic and IHG resistance exercise.

Specific Aims and Hypotheses

Specific Aim 1 To examine the BP lowering effects of acute and chronic aerobic compared to acute and chronic IHG resistance exercise among adults with high BP.

Hypothesis 1 BP will be lowered to greater levels following IHG resistance exercise than aerobic exercise, with respect to both acute exercise and exercise training.

Alternative Hypothesis 1 BP will be lowered to the same or lesser levels following IHG resistance exercise than aerobic exercise, with respect to both acute exercise and exercise training.

Specific Aim 2 To examine central arterial stiffness changes before and after acute and chronic aerobic and IHG resistance exercise among adults with high BP.

Hypothesis 2 Carotid-femoral PWV will be lowered to greater levels following IHG resistance exercise than aerobic exercise, with respect to both acute exercise and exercise training.

Alternative Hypothesis 2 Carotid-femoral PWV will be lowered to the same or lesser levels following IHG resistance exercise than aerobic exercise, with respect to both acute exercise and exercise training.

Specific Aim 3 To examine the correlation between BP and central arterial stiffness changes before and after acute and chronic aerobic and IHG resistance exercise among adults with high BP.

Hypothesis 3 Changes in carotid-femoral PWV after versus before aerobic and IHG resistance exercise will correlate with changes in BP after versus before aerobic and IHG resistance exercise, with respect to both acute exercise and exercise training.

Alternative Hypothesis 3 Changes in carotid-femoral PWV after versus before aerobic and IHG resistance exercise will be independent of changes in BP after aerobic and IHG resistance exercise, with respect to both acute exercise and exercise training.

Significance of Study

The AHA systematic review of the limited literature on the antihypertensive effects of IHG resistance exercise[22] suggests that the ACSM exercise prescription recommendations for hypertension[8] may warrant expansion to include IHG as a viable, alternative exercise modality to aerobic exercise to lower BP. The BP reductions of 3 to 19 mmHg that have been reported with IHG resistance exercise[23-28, 31] compared to 5 to 7 mmHg[8] with aerobic exercise suggest IHG may be more effective antihypertensive lifestyle therapy than aerobic exercise. Furthermore, IHG is relatively inexpensive[24], involves easily portable equipment, minimizes the musculoskeletal problems that can result for aerobic exercise, and requires less time than does aerobic exercise[24-26]. Aerobic exercise confers numerous health benefits in addition to lower BP and should not be discouraged. Nevertheless, IHG may be an attractive alternative to aerobic exercise for individuals with hypertension who have difficulty adhering to aerobic exercise regimes for a variety of reasons that may include boredom[19], lack of accessibility[19], and injury or disability[20, 21].

The goal of our research is to determine the most effective exercise prescription to prevent, treat and control hypertension. If our hypotheses prove correct, the findings from the proposed study will identify a more effective, time efficient antihypertensive therapeutic option for people with hypertension that also has the potential to improve adherence to exercise as antihypertensive lifestyle therapy. The new knowledge gained from this study will: 1) Advance the prescription of exercise to prevent, treat and control hypertension; 2) Enable exercise to take on increased importance as antihypertensive therapy; and 3) Provide valuable insight into mechanisms underlying the BP response to exercise.

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Preface

Chapter 2 provides information about the antihypertensive effects of aerobic versus isometric handgrip resistance exercise in the format to be submitted for publication. Additional details and explanation about the methods used in the study are printed in Chapter 3 and a fuller discussion of the results is presented in Chapter 4.

THE ANTIHYPERTENSIVE EFFECTS OF AEROBIC VERSUS ISOMETRIC HANDGRIP EXERCISE

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ABSTRACT

Aerobic exercise reduces blood pressure (BP) among those with hypertension, while limited evidence suggests similar BP benefits may result from isometric handgrip (IHG) resistance exercise. We compared the antihypertensive effects of an acute bout of aerobic compared to IHG exercise in the same group of people. Overweight adults with prehypertension (n=27) randomly completed three experiments: aerobic [60% peak oxygen uptake (VO_2peak), 30 minutes]; IHG [30% maximum voluntary contraction (MVC), 4x2 minutes bilateral]; and non-exercise control. Subjects left the laboratory wearing an ambulatory BP monitor. Systolic and diastolic BP (SBP/DBP) were lower after aerobic versus IHG (5.2±1.7/3.5±1.3mmHg, p=0.01) and control (6.8±1.9/5.4±1.4mmHg, p=0.001) over the awake hours, with no difference between IHG versus control (p>0.05). Clinical correlates accounted for 31.0 to 53.8% of the variability in BP response to aerobic that included dipper status, homeostatic model assessment of insulin resistance (HOMA), VO_2peak, peak SBP change to maximal exercise, ambulatory arterial stiffness (r=0.352), and resting BP (r=-0.272-0.326). Clinical correlates accounted for 18.2 to 49.2% of the variability in BP response to IHG that included nitrites/nitrates, HOMA, resting BP, and VO_2peak. A subset of participants then randomly completed either 8 weeks of aerobic (n=6, 60% VO_2peak, 45 min•day^{-1}) or IHG (n=5, 30% MVC, 4x2 minutes bilateral) training. Awake SBP was lower after versus before aerobic training (7.6±2.0 mmHg, p=0.02), while sleep DBP was higher after IHG training (7.5±1.8 mmHg, p=0.03). Our findings indicate that aerobic exercise is superior to IHG as antihypertensive therapy and should continue to be recommended for its immediate and sustained BP benefits.

INTRODUCTION

Hypertension is a major risk factor for cardiovascular disease affecting 33% of American adults (80 million)[1], a percent that has stabilized over the last 15 years[2]. Lifestyle factors are important modifiable determinants of hypertension[2]. Acute (short-term or postexercise hypotension [PEH]) and chronic (long-term or training) aerobic exercise lowers BP 5 to 7 mmHg among adults with hypertension. Therefore, the American College of Sports Medicine (ACSM) recommends adults with high BP perform 30 to 60 minutes of moderate intensity aerobic exercise on most, preferably all days of the week[3]. Unfortunately, the majority of people with hypertension do not adhere to the ACSM exercise recommendations to lower their high BP[1, 4].

Recent evidence suggests that isometric handgrip (IHG) resistance exercise may be an attractive, affordable, and accessible exercise modality for people with high BP[5]. For, several randomized controlled trials have indicated that the BP reductions that result from acute (i.e., PEH)[6] and chronic (i.e., training)[7-11] IHG resistance exercise appear to be equal to or even greater than those that result from aerobic exercise. Millar et al[6] reported an acute IHG session reduced BP 4 to 5 mmHg over 30 minutes in the laboratory among older men with normal BP. In addition, five studies[7-11] reported 8 to 10 weeks of IHG training for three days per week reduced BP 3 to 15 mmHg among young [9, 11] and older[7, 8, 10] adults with normal[7, 11] and high BP[8-10]. In contrast, Olher et al[12] reported that BP was not different after versus before acute IHG resistance exercise over 60 minutes in the laboratory among older women with high BP. In agreement with Olher et al[12], Stiller-Moldovan et al[13] reported that BP was not different after than before eight weeks of IHG training among older men and women with high BP. Given this

limited and mixed literature on the BP lowering effects of IHG resistance exercise, the American Heart Association (AHA) cautioned more data are needed to establish the efficacy and safety of IHG resistance exercise as antihypertensive therapy[5].

The primary purpose of our study was to compare the magnitude and duration of PEH after an acute bout of IHG resistance compared to aerobic exercise in the same group of adults in the early stages of hypertension. We hypothesized IHG resistance would elicit PEH to the same or even greater levels than aerobic exercise. In addition, we sought to examine clinical correlates that might provide insight into the mechanisms by which acute IHG and aerobic exercise may differentially exert their antihypertensive benefits.

METHODS

Subjects

Sedentary subjects aged 18 to 55 years with pre- to stage 1 hypertension and a body mass index (BMI) ≥25 to <40kg•m^{-2} were enrolled. Any medications that could potentially influence BP including inhaled or oral steroids, nonsteroidal anti-inflammatory agents, aspirin, antihypertensive and hyperlipidemic medications, nutritional supplements besides one-a-day vitamin, cold medications, hormone-altering contraception, or herbal supplements were stopped at least four weeks before any testing. If subjects were taking antihypertensive medications, they needed to express willingness to discontinue these medications with physician permission throughout the study. Four participants discontinued their antihypertensive medications to participate in the study. Exclusion criteria were: symptomatic atherosclerotic cardiovascular disease, diabetes mellitus, asthma, thyroid dysfunction, pancreatitis, acute illness, on

medication for depression, smoke, acute illness, two or more alcoholic drinks per day, an expressed desire to lose weight as a result of study participation, and physical limitations to perform exercise. We also discontinued two subjects whose weight changed ≥5 lb during the study. Women were pre-menopausal, not pregnant, and regularly menstruating. Subjects signed an informed consent form approved by the institutional review boards of the University of Connecticut and Hartford Hospital indicating their willingness to participate.

Procedures

This study was a randomized controlled crossover trial (Figure 1)[14-16]. Body weight was measured at each study visit to ensure weight maintenance. The female subjects logged their menstrual cycle to ensure that all testing would be performed in the follicular phase (days 1 to 10). A trained investigator (GIA) measured resting BP at each visit with an automated BPTRU BPM-100 monitor (Coquitlam, Canada) according to AHA standards[17]. At the end of each visit, this investigator attached an Oscar2 ambulatory BP monitor (SunTech Medical, Raleigh, NC) to the subject's non-dominant arm. The subject left the laboratory, proceeded with normal activities, and returned the monitor the next morning[14-18]. Ambulatory BP studies from Visits 1 through 3 were used to familiarize subjects with the technology[18], and confirm that they met the inclusion criteria of having pre- to stage 1 hypertension.

Subjects then completed two peak graded exercise stress tests (GEST, Visits 2-3, Figure 1). The purpose of the first GEST was to exclude atherosclerotic ischemic heart disease; while the second was to determine peak oxygen uptake (VO_{2peak}) by cycling continuously at a constant cadence of 60 revolutions per minute with resistance

increased by 0.5 kiloponds every 2 minutes until volitional exhaustion[19]. Subjects also provided a fasting blood sample (Visit 3, Figure 1) for baseline values of serum lipids, lipoproteins, glucose, insulin, and nitrite (NO_2^-)/ nitrate (NO_3^-) (Methods Supplement #1). To measure PEH, subjects completed three experiments in random order at the same time of the morning at least 48 hours apart (Visits 4 through 6, Figure 1). Subjects were instructed to consume a standard breakfast 3 hours before all experiments and refrain from caffeinated beverages[14-16]. Each experiment began with 10 minutes of supine rest followed by a baseline measurement of pulse wave velocity (PWV), an index of arterial stiffness (Methods Supplement #2). Volunteers then sat for 20 minutes with BP recordings taken every 2 minutes from the non-dominant arm, which were averaged to determine baseline BP.

The three randomized experiments included: 1) Aerobic Exercise- cycling for 20 minutes at 60% VO_{2peak} with a 5 minute warm up and cool down to total 30 minutes. Intensity was monitored using a Polar Heart Rate Monitor (Lake Success, NY) based upon a linear regression plot of work and heart rate versus VO_2 achieved on the cardiopulmonary GEST; 2) IHG Resistance Exercise- a digital handgrip device (Zonaplus, Boise, ID) was held while sitting upright in a chair with feet flat on the floor, and a single maximal contraction of the hand flexor muscles with each hand was completed to determine MVC. Subjects then performed four, 2 minute alternating bilateral contractions of the hand flexor muscles at 30% MVC with 1 minute rest between contractions[6, 20]. Subjects were provided feedback and encouragement to sustain 30% MVC. The percentage of time they held this tension was registered by the digital device and averaged 85.1±1.5%; and 3) Control- sitting quietly for 30 minutes.

All experiments concluded with 30 minutes of seated recovery followed by 30 minutes of supine recovery, with BP and PWV measured at designated time points. Subjects left the laboratory wearing the same ambulatory BP monitor as they wore during the screening Visits 1 through 3 until the next morning.

After completion of the PEH experiments, 11 of the 27 subjects volunteered to participate in an exercise training program to investigate whether aerobic versus IHG resistance exercise training influenced resting BP and/or PEH (Figure 1). These individuals completed a four week wait list control period[21], after which systolic/diastolic BP (SBP/DBP) were not different than before the wait list control period ($p>0.05$). The subjects were then randomly assigned to complete either a supervised aerobic (n=6, 60% VO_2peak, 45 minutes per day) or IHG (n=5, 30% MVC, 4x2 minutes bilateral) exercise training program three days per week for eight weeks (Methods Supplement #3). During the last week of training, each subject completed a post-training cardiopulmonary GEST (Visit 7, Figure 1). Then, we reassessed PEH (Figure 1, Visits 8 & 9) following the identical protocol of the pre-training PEH experiments, with the intensity of aerobic exercise monitored based upon results of the post-training cardiopulmonary GEST. Visits 7 through 9 were each separated by 48 hours, which was long enough to avoid the confounding effects of PEH from the previous session[22], but short enough to avoid the confounding effects of detraining on BP[23, 24].

Statistical Analysis

Data are reported as mean ± standard error. Repeated measures analysis of covariance (RMANCOVA) compared BP over hourly intervals between experiments (control, aerobic, and IHG) and before versus after training with age and BMI as

covariates over awake (1 to 10 hours post-exercise), sleep (11 to 19 hours), and 19 hours. PEH was calculated before and after training as the BP change following control versus the BP change following exercise (aerobic and IHG) at hourly intervals. The resting BP response to exercise training was calculated as ambulatory BP over awake, sleep, and 19 hours on the day of the resting control experiment before versus after training at hourly intervals. Multiple variable linear regression examined clinical correlates of PEH and the resting BP response to exercise training.

We established minimum statistical power β=80% and significance α=0.05. Based upon previous literature, we expected SBP reductions of 6.9±1.1 mmHg[25] and 13.4±1.1 mmHg[26] following aerobic and IHG exercise respectively, requiring n=24 subjects to test the hypothesis that PEH magnitude would differ by modality. To detect clinical correlates of PEH, based on our previous work[27], we expected r^2=0.30 attributed to two significant independent variables and r^2=0.20 attributed to eight other independent variables, requiring n=22 subjects to detect clinical correlates. Thus, a sample size of 27 subjects was adequately powered to compare PEH by modality as well as assess clinical correlates of PEH, although the sample size for the training groups (aerobic n=6, IHG n=5, Figure 1) was not. However, power among the training groups was increased by employing mixed linear models with hourly intervals as an alternative to RMANOVA; thus representing each subject as 19 hourly BP measurements and making the effective sample size n=5x19=95. All statistical analyses utilized SPSS 14.0 (Chicago, IL) except for mixed linear models (SAS 9.3, Cary, NC) and power calculations (SAS 9.3 and PASS 2008, NCSS, Kaysville, UT).

RESULTS

Subjects

Subjects were overweight to obese with prehypertension and of below average physical fitness for their age[28] (Table 1), while fasting glucose[29] and lipids-lipoproteins[30] were within normal ranges (Table 2). Over half (52%) of the participants reported a family history of hypertension among first degree relatives. Baseline subject characteristics did not differ between the exercise modality groups ($p>0.05$). Exercise training performance and outcomes are detailed in Results Supplement #1.

Postexercise Hypotension (PEH) before Training

After acute aerobic exercise, SBP increased by 14.0±2.1 mmHg from a baseline of 121.4±2.0 mmHg ($p<0.001$), while DBP was not different from a baseline of 80.1±1.4 mmHg ($p>0.05$) over 19 hours. Nonetheless, SBP and DBP increased 4.0±1.5/3.6±1.0 mmHg less after aerobic exercise compared to control over 19 hours ($p=0.02$/$p=0.002$) and awake (6.8±1.9/5.4±1.4 mmHg, $p=0.001$/$p=0.001$) (Figure 2). In contrast, sleep SBP and DBP were not different after versus before aerobic exercise compared to control ($p>0.05$) (Figure 2).

After acute IHG resistance exercise, SBP and DBP increased by 16.3±2.0/3.2±1.2 mmHg from a baseline of 120.1±1.9/77.9±1.3 mmHg ($p<0.001$/$p=0.01$) over 19 hours. SBP and DBP were not different after versus before IHG compared to control over 19 hours, awake, or sleep ($p>0.05$) (Figure 2). Furthermore, DBP over 19 hours (3.6±1.0 mmHg, $p=0.04$) and SBP and DBP over awake (5.2±1.7/3.5±1.3 mmHg, $p=0.01$/0.01) increased less after versus before aerobic exercise compared to IHG (Figure 2).

Postexercise Hypotension (PEH) after Training

After acute aerobic exercise (n=6), SBP increased by 20.5±5.5 mmHg from a baseline of 117.2±3.0 mmHg (p=0.01), while DBP was not different from a baseline of 79.0±2.3 mmHg (p>0.05) over 19 hours after exercise training. SBP and DBP were not different after versus before acute aerobic exercise compared to control over 19 hours, awake, or sleep (p>0.05) (Figure 3) after exercise training. The magnitude of PEH over awake after acute aerobic exercise (Figure 3) was attenuated by 9.3±3.4/6.6±3.0 mmHg after versus before training (p=0.04/0.01) (Figure 2). However, PEH over 19 hours and sleep were not different after (Figure 3) versus before training (Figure 2) (p>0.05).

After acute IHG resistance exercise (n=5), SBP increased by 14.1±2.5mmHg from a baseline of 118.4±1.9 mmHg (p=0.01), while DBP was not different from a baseline of 77.7±2.0 mmHg (p>0.05) after training. SBP and DBP changes were not different after versus before acute IHG resistance exercise compared to control over 19 hours, awake, or sleep (Figure 3) (p>0.05) after training. PEH over 19 hours, awake, and sleep was not different after (Figure 3) versus before training (Figure 2) (p>0.05).

Resting Blood Pressure Response to Exercise Training

After aerobic exercise training (n=6), resting 19 hour (4.2±1.4 mmHg, p=0.04) and awake (7.6±2.0 mmHg, p=0.02) SBP were lower than before training, but resting 19 hour DBP, awake DBP, and sleep SBP and DBP were not different than before training (p>0.05) (Figure 4). After IHG resistance exercise training (n=5), resting awake SBP and DBP and sleep SBP were not different than before training (p>0.05), but resting 19 hour SBP and DBP (5.0±1.5/4.9±1.1 mmHg, p=0.05/p=0.03) and resting sleep DBP (7.5±1.8 mmHg, p=0.03) were higher than before training (Figure 4). Moreover, resting

19 hour SBP (9.1±3.4 mmHg, p=0.03) and resting awake SBP and DBP (10.8±3.9/4.9±2.2 mmHg, p=0.02/p=0.05) decreased more after versus before aerobic exercise training than IHG exercise training (Figure 4).

Clinical Correlates of Postexercise Hypotension (PEH) before Exercise Training

Correlates of PEH after acute aerobic exercise accounted for 31.0% to 53.8% of the variability in the magnitude of PEH (Table 3). The subjects that experienced the BP reductions of the greatest magnitude after acute aerobic exercise were nocturnal BP dippers (r=-0.465 to -0.526), had lower baseline homeostatic model assessment of insulin resistance (HOMA, r=0.467 to 0.494), higher VO_{2peak} (r=-0.374), a lower peak SBP response to a GEST (r=0.324 to 0.355), higher baseline BP (r=-0.272 to -0.326), and higher ambulatory arterial stiffness index (r=-0.352); compared to participants that were not dippers, had higher baseline HOMA, lower VO_{2peak}, a higher peak SBP response to a GEST, lower baseline BP, and lower ambulatory arterial stiffness index.

Correlates of the BP response to acute IHG resistance exercise accounted for 18.2% to 49.2% of the variability in the magnitude of the BP change. The subjects that experienced the BP increases of the greatest magnitude after acute IHG resistance exercise had lower baseline NO_2^-/NO_3^- (r=-0.472), higher baseline HOMA (r=0.397 to 0.431), lower baseline BP (r=-0.427), and lower VO_{2peak} (r=-0.288 to -0.411); compared to participants that had higher baseline NO_2^-/NO_3^-, lower baseline HOMA, higher baseline BP, and higher VO_{2peak}.

DISCUSSION

We compared the BP response to acute aerobic and IHG resistance exercise among young and middle-aged adults with prehypertension in a randomized cross over

design. In a subset of these people, we also examined changes in resting BP after 8 weeks of either aerobic or IHG resistance exercise training. Our major finding was acute aerobic exercise lowered BP 5 to 7 mmHg after acute and chronic aerobic exercise, while BP was not different after acute IHG resistance exercise, and became 5 to 7 mmHg higher after than before IHG training compared to control. Contrary to our hypothesis, acute and chronic IHG resistance exercise were not superior to acute and chronic aerobic exercise in lowering ambulatory BP over 19 hours. In fact, BP was 4 to 5 mmHg lower after than before acute aerobic versus IHG exercise, and resting BP was 6 to 11mmHg lower after versus before aerobic versus IHG exercise training.

Our findings are in agreement with two reports that acute[12] and chronic[13] IHG resistance exercise did not lower BP, while they are in contrast with others that concluded acute and chronic IHG resistance exercise reduced BP to the same or greater levels as acute[6] and chronic[7-11] aerobic exercise. Discrepancies between our study and these other reports[6-11] may be partially attributed to differences in study design. Strengths of our study were that it was the first randomized crossover trial examining PEH following IHG resistance versus aerobic exercise compared to control among the same individuals with high BP. Furthermore, our study sample was over twice the size of previous studies examining the antihypertensive effects of acute IHG[6, 12]. Therefore, the unique features of our randomized controlled trial in which subjects served as their own control have influenced the difference in outcomes. Last, other study design features such as differences in the demographic characteristics of the study populations[6-13], and IHG protocols[12] may have contributed to discrepancies in this literature.

It is interesting to note that in the only other study examining the antihypertensive effects of IHG exercise with ambulatory BP monitors. Stiller-Moldovan et al found ambulatory BP was not different after versus before IHG training[13], a finding consistent with ours. All reports except one[12] that found BP was lowered after acute[6] and chronic[7-11] IHG measured auscultatory BP in the laboratory. These observations suggest that the antihypertensive effects of IHG observed in the laboratory[6-11] may not persist under conditions of daily living.

A growing body of evidence indicates that health outcomes following exercise exhibit inter-individual variability that is belied by mean results[25, 31]. For example, the standard deviation of the change in a variety of cardiovascular disease risk factors following aerobic exercise training in the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) study (n=723)[32] exceeded the mean value of the change that included BP. In a recent meta-analysis of randomized controlled trials of the BP change following IHG resistance exercise training[20] , the standard deviation also exceeded the mean value of the change. We also found the standard deviation of the BP change following acute aerobic (-6.8±9.8 mmHg, Figure S1) and acute IHG exercise (-1.6±8.8 mmHg, Figure S2) exceeded the mean value of the change. Furthermore, 10 of the 27 participants in our study did not achieve clinically significant antihypertensive benefit (SBP and DBP reduced by ≥2 mmHg) following acute aerobic exercise (Figure S1); while 13 did achieve such benefit following IHG (Figure S2). Nonetheless, ambulatory BP was on average 5 mmHg lower after acute aerobic than acute IHG exercise. In addition, most of the participants (i.e., 85%) individually experienced a greater BP reduction following acute aerobic than acute IHG exercise, reinforcing our major finding

that acute aerobic was superior to acute IHG exercise in lowering ambulatory BP throughout the day time hours.

One factor that can partially account for variability in the BP response to exercise is technical error related to obtaining repeated measurements[32]. We took considerable care to minimize technical error by having all BP assessments performed by a single investigator (GIA) at the same time of day using the same ambulatory BP monitor for the same subject throughout study duration. As a result, the coefficients of variation for baseline SBP/DBP before the acute experiments for a given subject were 2.9%/3.5%, respectively. Thus, technical error did not appear to be a predominant factor influencing variability in the BP response to exercise among our participants.

However, we found that clinical correlates (Table 3) explained 31-54% of the intra-individual variability in the BP response following acute aerobic exercise that included nocturnal BP dipper status[33], HOMA[34], VO_{2peak}[35], the peak SBP response to a GEST[36], and resting BP[14-16]. Consistent with these findings, we and others have found that nocturnal dipper status[33], insulin sensitivity[16, 37], cardiorespiratory fitness level[38], the peak SBP response to a GEST[36, 37], and resting BP[38, 39] accounted for a clinically meaningful proportion of the variability in the BP response to acute aerobic exercise. We also found that resting BP[40], baseline NO_2^-/NO_3^-, HOMA, and VO_{2peak} accounted for 18-49% of the variability in the BP response to acute IHG. These correlates have been shown to be associated with important regulatory factors that influence resting BP as well as the BP response to exercise such as SNA[41, 42], activity of the renin-angiotensin system[41, 43, 44], endothelial function[45, 46], oxidative stress[47], and inflammation[48]. Nonetheless, there is a large proportion of the variability in the BP response

unexplained indicating the need for further investigation to gain better insight into mechanisms underlying cardiovascular adaptations to exercise.

Acute aerobic and IHG resistance exercise both increase central sympathetic nerve activity (SNA) during exercise through mechanical and chemical stimulation of afferent muscle neurons[49-54]. However acute aerobic exercise has been widely demonstrated to promote accumulation of muscle metabolites (ATP, potassium ions, hydrogen ions) and release of vasodilators from the endothelium (nitric oxide, prostaglandins), all of which reduce alpha-adrenergic responsiveness and increase vascular conductance during and after exercise[49-51]. These changes, termed *functional sympatholysis*, are specific to exercising muscles and therefore occur systemically following aerobic but not IHG resistance exercise. In fact, IHG elicits an "open-loop" feedback in which vasoconstriction elicited by mechanical and chemical stimulation of afferent muscle neurons, mechanical torsion of isometrically contracting muscles, and subsequent reductions in blood flow and vascular shear stress promote increased BP[55-60]. Furthermore this response is augmented among individuals with high resting BP[52-54]. Therefore, this literature is consistent with our findings that aerobic exercise is superior antihypertensive lifestyle therapy than IHG resistance exercise. It is also noteworthy since BP was not different following acute IHG (Figure 2) but higher following IHG training (Figure 4) that different mechanisms may govern the acute versus chronic BP response to IHG. An intervention like IHG that induces discomfort acutely reduces BP sensitivity to painful sensastions[61] which could partially counteract the unfavorable influence of IHG upon SNA and BP[52-54], but repeated bouts as in IHG exercise training can reverse this effect due to dysfunction of the release of opioids[61].

PEH appears to account for some, if not all, of the antihypertensive effects of more long-term exercise training, for previous studies have found the two are strongly correlated[62, 63]. We too found PEH was correlated with the BP response to exercise training (Results Supplement #2), but this association was not significant in multiple variable models adjusted for pre training resting BP (Table S1). Further studies should test this supposition among a larger sample size.

Strengths and Limitations

Although this study bore methodological strengths including a randomized controlled crossover design and the clinical gold standard assessment of ambulatory BP [17], it was not without limitations. We were adequately powered to compare the antihypertensive effects of acute aerobic versus IHG resistance exercise and furthermore assess its clinical correlates. Yet, the subpopulations completing the aerobic (n=6) and IHG resistance exercise training (n=5) portion of our study were underpowered so that these findings should be treated with caution.

PERSPECTIVES

Our findings support the recommendations of the ACSM[3] as well as the AHA[5] and other professional organizations[64, 65] that aerobic exercise should be the primary modality of choice among adults with high BP for its immediate and sustained BP lowering effects. Caution is warranted at this time regarding the efficacy of acute and chronic IHG resistance exercise as antihypertensive therapy, considering our findings that aerobic exercise elicited greater PEH than IHG in almost all participants (85%). Nonetheless, our findings are intriguing due to strength of our randomized cross over design and warrant confirmation, especially regarding how the BP response to acute

aerobic exercise translates into the long-term BP response to exercise training.

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DISCLOSURES

None.

FIGURE LEGENDS

Figure 1. Study Design. *Blood pressure measured throughout (see text for details). †Ambulatory blood pressure monitor worn afterwards until waking the next morning. ‡Pulse wave velocity measured throughout (see text for details). GEST, graded exercise stress test. MVC, maximum voluntary contraction. VO_{2peak}, peak oxygen consumption.

Figure 2. Postexercise hypotension before exercise training (n=27). Postexercise hypotension was defined as mean (±SEM) systolic/diastolic blood pressure (SBP/DBP) change following control subtracted from SBP/DBP change following acute exercise over awake, sleep, and 19 hours. □ Acute Aerobic Exercise. ■ Acute Isometric Handgrip Resistance Exercise. *p≤0.05 vs isometric handgrip, †p≤0.05 vs control.

Figure 3. Postexercise hypotension after exercise training. Postexercise hypotension was defined as mean (±SEM) systolic/diastolic blood pressure (SBP/DBP) change following control subtracted from SBP/DBP change following acute exercise over awake, sleep, and 19 hours. □ Aerobic Exercise (n=6). ■ Isometric Handgrip Resistance Exercise (n=5). ‡p≤0.05 vs Postexercise hypotension before training.

Figure 4. Mean (±SEM) resting systolic/diastolic blood pressure (SBP/DBP) response to exercise training over awake, sleep, and 19 hours. Resting blood pressure response to exercise training was defined as average resting blood pressure before training subtracted from average resting blood pressure after training. □ Aerobic Exercise (n=6). ■ Isometric Handgrip Resistance Exercise (n=5). *p≤0.05 vs isometric handgrip, ‡p≤0.05 vs pre-training.

Table 1. Mean (±SEM) demographic and blood pressure characteristics of the subjects (n=27).

Age (yr)	40.6±2.0
Race (African American / Caucasian / Other)	15 / 10 / 2
Gender (male / female)	23 / 4
Body mass index ($kg \cdot m^{-2}$)	30.7±0.7
Waist circumference (cm)	91.6±1.8
Relative peak oxygen consumption ($mL \cdot kg^{-1} \cdot min^{-1}$)	27.4±1.1
19 hour systolic blood pressure (mmHg)	138.4±1.9
19 hour diastolic blood pressure (mmHg)	82.9±1.5
Awake systolic blood pressure (mmHg)	145.7±2.0
Awake diastolic blood pressure (mmHg)	89.4±1.5
Sleep systolic blood pressure (mmHg)	130.3±2.3
Sleep diastolic blood pressure (mmHg)	75.7±1.9
Dipper / Non-Dipper	15 / 12
Ambulatory arterial stiffness index	0.393±0.025

Table 2. Mean (SEM) cardiometabolic characteristics of the subjects

(n=26)

Fasting glucose ($mmol \cdot L^{-1}$)	5.39±0.11
Fasting insulin ($pmol \cdot L^{-1}$)	70.8±10.4
HOMA	2.4±0.3
Fasting low-density lipoproteins ($mmol \cdot L^{-1}$)	2.958±0.150
Fasting high-density lipoproteins ($mmol \cdot L^{-1}$)	1.269±0.070
Fasting triglycerides ($mmol \cdot L^{-1}$)	1.294±0.157
Nitrite (NO_2^-) + Nitrate (NO_3^-) ($\mu mol \cdot L^{-1}$)	15.24±4.66

HOMA, Homeostatic Model Assessment of Insulin Resistance.

One subject declined to provide a blood sample, so these parameters were measured for the other 26 subjects.

Table 3. Multiple variable regression models identifying clinical correlates of postexercise hypotension following acute aerobic exercise before training among adults with prehypertension (n=26). Postexercise hypotension was defined as blood pressure change following control subtracted from blood pressure change following exercise.

Variable	β (±SE)	Partial r^2	*p*
Awake Systolic Blood Pressure			
Dipper	-11.027±3.270	0.277	0.01
Baseline systolic blood pressure	-0.306±0.154	0.106	0.06
Total Model		**0.383**	**0.004**
Awake Diastolic Blood Pressure			
Dipper	-6.989±2.582	0.216	0.01
Baseline diastolic blood pressure	-0.332±0.177	0.095	0.09
Total Model		**0.310**	**0.014**
Sleep Systolic Blood Pressure			
Baseline HOMA	2.110±0.869	0.218	0.02
Peak systolic blood pressure	0.141±0.067	0.126	0.05
Total Model		**0.344**	**0.008**
Sleep Diastolic Blood Pressure			
Baseline HOMA	1.471±0.492	0.244	0.01
Ambulatory arterial stiffness	-16.507±6.526	0.124	0.02
Peak systolic blood pressure change to a GEST	0.083±0.038	0.112	0.04
Total Model		**0.480**	**0.002**
19 Hour Systolic Blood Pressure			
Baseline HOMA	2.239±0.689	0.219	0.004
Peak systolic blood pressure	0.157±0.061	0.105	0.02
Peak oxygen uptake	-0.689±0.240	0.140	0.01
Baseline systolic blood pressure	-0.226±0.123	0.074	0.08
Total Model		**0.538**	**0.002**
19 Hour Diastolic Blood Pressure			
Baseline HOMA	1.351±0.523	0.246	0.02
Baseline diastolic blood pressure	-0.238±0.130	0.095	0.08
Total Model		**0.342**	**0.008**

HOMA, Homeostatic Model Assessment of Insulin Resistance.

GEST, Graded Exercise Stress Test.

BP dipper status (SBP and DBP fall ≥10% of daytime values)[66] and ambulatory arterial stiffness index [1 – (slope of DBP vs SBP over 19 hours]][67] were calculated using the resting control experiment before training (Figure 1). Results are displayed as reduced models with only significant predictors retained.

Table 4. Multiple variable regression models identifying clinical correlates of postexercise hypotension following acute isometric handgrip resistance exercise before training among adults with prehypertension (n=26). Postexercise hypotension was defined as blood pressure change following control subtracted from blood pressure change following acute exercise.

Variable	β (±SE)	Partial r^2	*p*
Awake Systolic Blood Pressure			
Baseline HOMA	3.378±0.848	0.186	0.001
Baseline Nitrite + Nitrate	-0.143±0.069	0.223	0.05
Peak oxygen uptake	-0.489±0.258	0.083	0.07
Total Model		**0.492**	**0.002**
Awake Diastolic Blood Pressure			
Baseline HOMA	1.597±0.604	0.158	0.02
Peak oxygen uptake	-0.359±0.182	0.122	0.06
Total Model		**0.280**	**0.02**
Sleep Systolic Blood Pressure			
No significant correlates			
Sleep Diastolic Blood Pressure			
Baseline diastolic blood pressure	-0.412±0.178	0.182	0.03
Total Model		**0.182**	**0.03**
19 Hour Systolic Blood Pressure			
Baseline HOMA	2.290±0.750	0.183	0.01
Peak oxygen uptake	-0.552±0.225	0.169	0.02
Total Model		**0.352**	**0.007**
19 Hour Diastolic Blood Pressure			
Baseline HOMA	1.441±0.506	0.176	0.01
Peak oxygen uptake	-0.322±0.152	0.134	0.05
Total Model		**0.310**	**0.01**

HOMA, Homeostatic Model Assessment of Insulin Resistance.

Results are displayed as reduced models with only significant predictors retained.

Figure 1

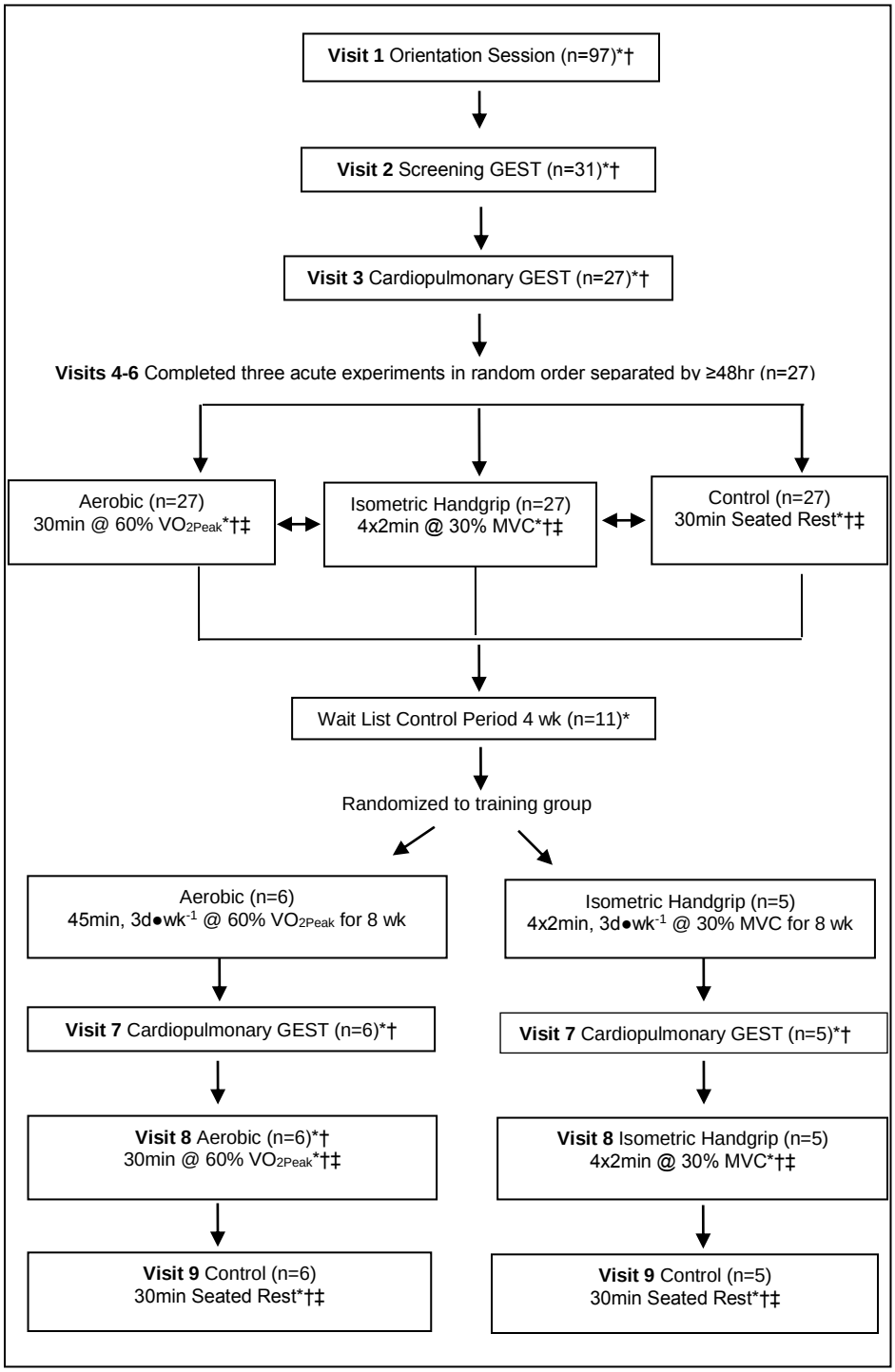

Visit 1 Orientation Session (n=97)*†
Visit 2 Screening GEST (n=31)*†
Visit 3 Cardiopulmonary GEST (n=27)*†
Visits 4-6 Completed three acute experiments in random order separated by ≥48hr (n=27)
Aerobic (n=27)
30min @ 60% VO_{2Peak}*†‡
Isometric Handgrip (n=27)
4x2min @ 30% MVC*†‡
Control (n=27)
30min Seated Rest*†‡
Wait List Control Period 4 wk (n=11)*
Randomized to training group
Aerobic (n=6)
45min, 3d●wk^{-1} @ 60% VO_{2Peak} for 8 wk
Isometric Handgrip (n=5)
4x2min, 3d●wk^{-1} @ 30% MVC for 8 wk
Visit 7 Cardiopulmonary GEST (n=6)*†
Visit 7 Cardiopulmonary GEST (n=5)*†
Visit 8 Aerobic (n=6)*†
30min @ 60% VO_{2Peak}*†‡
Visit 8 Isometric Handgrip (n=5)
4x2min @ 30% MVC*†‡
Visit 9 Control (n=6)
30min Seated Rest*†‡
Visit 9 Control (n=5)
30min Seated Rest*†‡

Figure 2

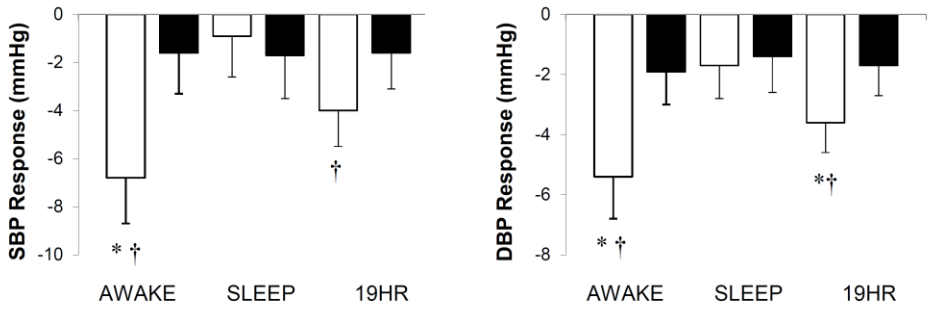


Figure 3

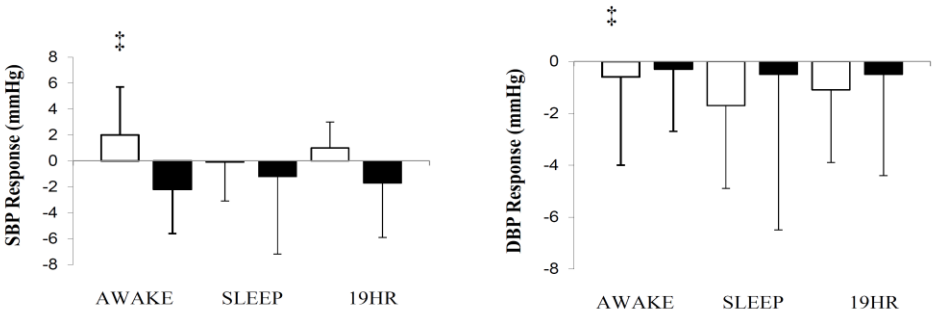
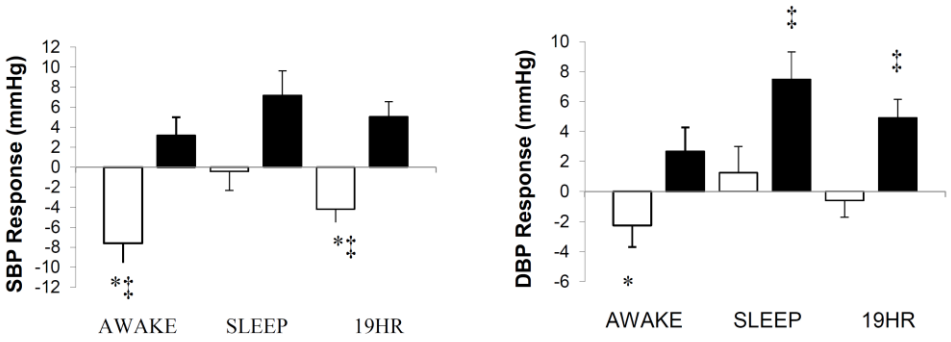


Figure 4



ONLINE SUPPLEMENT

Methods Supplement #1--Blood Sampling and Analysis

Fasting blood samples were drawn without stasis from an antecubital vein using an indwelling catheter into red (no additive) and purple (potassium EDTA) top tubes. Blood samples were then centrifuged at 2500g and 23 °C for 15 minutes. Serum samples were transferred from red top tubes and plasma samples from purple top tubes into 1.8 mL non-pyrogenic storage tubes and frozen at -80 °C until analysis. Serum high density lipoprotein cholesterol, total cholesterol, triglycerides, glucose, and insulin were determined by colorimetric enzymatic assays (Quest Diagnostics, Wallingford, CT). Low density lipoprotein cholesterol was calculated with the Friedwald equation[68]. The homeostatic model assessment [HOMA, glucose ($mmol \cdot L^{-1}$) x insulin ($pmol \cdot L^{-1}$) x 156.3^{-1}] was calculated as a measure of insulin sensitivity[69]. Serum nitrite (NO_2^-) and nitrate (NO_3^-) levels were measured by colorimetric enzymatic assays (R&D Systems, Minneapolis, MN). All samples were run on a single assay by a trained investigator (KDB) with sensitivity 0.25 $\mu mol \cdot L^{-1}$ and coefficient of variation 9.1%[70].

Methods Supplement #2--Arterial Stiffness Assessment

A single trained investigator (GIA) measured carotid-femoral PWV, an index of central arterial stiffness; femoral-ankle PWV, an index of peripheral arterial stiffness; and central SBP[71] using the SphygmoCor® CPV Central Blood Pressure/Pulse Wave Velocity System (AtCor Medical; Sydney, Australia). Doppler waveforms at the carotid, femoral, and dorsalis-pedis arteries on the non-dominant side were assessed with a Millar tonometer. The average time difference between the Doppler waveforms and simultaneous electrocardiogram tracings was calculated over 10 seconds to determine

pulse transit time. Carotid-femoral pulse transit distance (from femoral pulse to sternal notch via the umbilicus minus the distance from carotid pulse to sternal notch) and femoral-ankle pulse transit distance (from femoral pulse to dorsalis pedis pulse) were divided by average pulse transit time to calculate central and peripheral PWV, respectively. Finally, central SBP was assessed by analysis of the radial pulse waveform transformed to the aortic pulse waveform using a generalized transfer function[71]. The day-to-day coefficient of variation was 5.3% for carotid-femoral PWV, 8.3% for femoral-ankle PWV, and 3.2% for central SBP.

Methods Supplement #3--Exercise Training

Body weight was obtained and BP was measured before and after each exercise training session. The aerobic exercise group exercised on a cycle ergometer with the duration of each session progressing from 15 to 40 minutes during the first four weeks of training and remained at 40 minutes for the next four weeks of training. An additional five minute warm-up and cool-down period were included so that each session totaled 25 to 50 minutes. The intensity of exercise was 40% to 60% VO_{2peak} during the first four weeks of training and progressed to 60-70% VO_{2peak} during the second four weeks. During exercise, heart rate from a Polar heart rate monitor was recorded onto standardized forms at five minute intervals, and the subject's Borg Rating of Perceived Exertion on the 6 to 20 scale[72] was recorded halfway through the session[73]. The isometric handgrip (IHG) resistance exercise group performed four, two minute alternating bilateral contractions of the hand flexor muscles at 30% MVC with one minute rest between contractions three days per week for eight weeks, with heart rate and the Borg Rating of Perceived Exertion on the 6 to 20 scale[72] recorded once during

the second and fourth contractions[73]. Each participant completed the timeline followback for exercise, a self-report calendar diary method for assessing daily exercise habits, through an interview style approach on a weekly basis[74]. These diaries were used to confirm the participants did not engage in exercise outside of supervised exercise sessions.

Methods Supplement #4--Statistical Analysis of the Arterial Stiffness Response to Acute Exercise and Exercise Training

RMANCOVA compared arterial stiffness dependent variables (carotid-femoral PWV, femoral-ankle PWV, and central SBP) over time (baseline, 35 minutes, and 60 minutes post-exercise) between experimental conditions (control, aerobic exercise and IHG) and before versus after training with age and BMI as covariates. The arterial stiffness response to acute exercise was calculated as the arterial stiffness change following control versus the arterial stiffness change following exercise. The resting arterial stiffness response to exercise training was calculated as the average pre-exercise baseline value across the acute experimental sessions before (Visits 4 through 6, Figure 1) versus after training (Visits 8 & 9, Figure 1).

RESULTS

Results Supplement #1--Exercise Training Outcomes

The aerobic exercise group cycled for 44.8±0.3 minutes per day at 63.3±0.8% VO_{2peak} for three days per week. The IHG resistance exercise group performed four, two minute bilateral IHG contractions per day at 30% MVC, sustaining this tension with an average adherence score of 87.3±5.3% for three days per week. All study participants regardless of group completed 100% of the required 24 training sessions.

After exercise training, VO_{2peak} increased by 2.3±0.8 $mL \cdot kg^{-1} \cdot min^{-1}$ among the aerobic exercise group (p=0.02), but was not different from baseline among the IHG resistance exercise group (p>0.05).

Results Supplement #2--Clinical Correlates of Resting Blood Pressure Response to Exercise Training

The subjects that experienced the BP reductions of the greatest magnitude after aerobic exercise training (n=5) had higher pre-training resting BP (β=-0.623 to -1.004), higher pre-training waist circumference (β=-1.273), higher pre-training NO_2^-/NO_3^- (β=-0.0191), greater decreases in HOMA following training (β=5.467 to 10.025), and greater increases in VO_{2peak} following training (β=-3.211). In addition, the resting SBP/DBP response to training correlated with PEH before training (r=0.469/0.523, p<0.01). While, pre-training resting SBP/DBP correlated with the resting SBP/DBP response to training (r=-0.482/-0.535, p<0.01) and with PEH before training (-0.625/-0.671, p≤0.01). In multiple variable models adjusted for pre-training resting SBP/DBP, the association of resting SBP/DBP response to training with PEH before training was not significant (Table S1).

The subjects that experienced the BP increases of the greatest magnitude after IHG resistance exercise training (n=5) had lower pre-training resting BP (β=-0.504 to -0.925), higher pre-training NO_2^-/NO_3^- (β=0.454 to 0.680), and lower pre-training ambulatory arterial stiffness index (β=-74.936). The resting SBP/DBP response to IHG training correlated with the SBP/DBP response to acute IHG (r=0.422/0.452, p<0.01). While, pre-training resting SBP/DBP correlated with the resting SBP/DBP response to IHG training (r=-0.337/-0.453, p<0.01) and with the SBP/DBP response to acute IHG

before training (r=-0.402/-0.342, p<0.01). In multiple variable models adjusted for pre-training resting SBP/DBP, the association of SBP/DBP response to acute IHG before training with the resting SBP/DBP response to IHG training was significant for sleep SBP (β=0.347) and 19 hour SBP (β=0.211), but not significant for awake SBP/DBP, sleep DBP, or 19 hour DBP (Table S2).

Results Supplement #3--The Arterial Stiffness Response to Acute Exercise before Training

After acute aerobic and IHG exercise (n=27, Visits 4-6, Figure 1), carotid-femoral PWV and femoral-ankle PWV were not different from baseline following control, aerobic exercise and IHG (p>0.05) (Table S3). Central SBP was lower following acute aerobic exercise versus control (-4.1±1.7 mmHg, p=0.03), but not different following acute IHG versus control (p>0.05). Furthermore, central SBP was lower following acute aerobic exercise versus IHG (-4.8±1.5 mmHg, p=0.004) (Table S3).

Results Supplement #4--The Resting Arterial Stiffness Response to Exercise Training

After aerobic exercise training (n=6), resting carotid-femoral PWV was lower than before training (-0.48±0.11 $m \cdot s^{-1}$, p=0.01) (Table S4). After IHG training (n=5), carotid-femoral PWV tended to be lower than before training (-0.50±0.20 $m \cdot s^{-1}$, p=0.07) (Table S4). The decrease in carotid-femoral PWV was not different following aerobic exercise training versus IHG training (p>0.05). After aerobic exercise training (n=6) and IHG training (n=5), femoral-ankle PWV and central SBP were not different than before training (p>0.05) (Table S4).

SUPPLEMENT FIGURE LEGENDS

Figure S1. Postexercise hypotension following acute aerobic exercise over awake hours ranked by individual subjects (n=27). Postexercise hypotension was defined as systolic blood pressure change following control subtracted from systolic blood pressure change following acute exercise.

Figure S2. Postexercise hypotension following acute isometric handgrip resistance exercise over awake hours ranked by individual subjects (n=27). Postexercise hypotension was defined as systolic blood pressure change following control subtracted from systolic blood pressure change following acute exercise.

SUPPLEMENT FIGURES

Figure S1

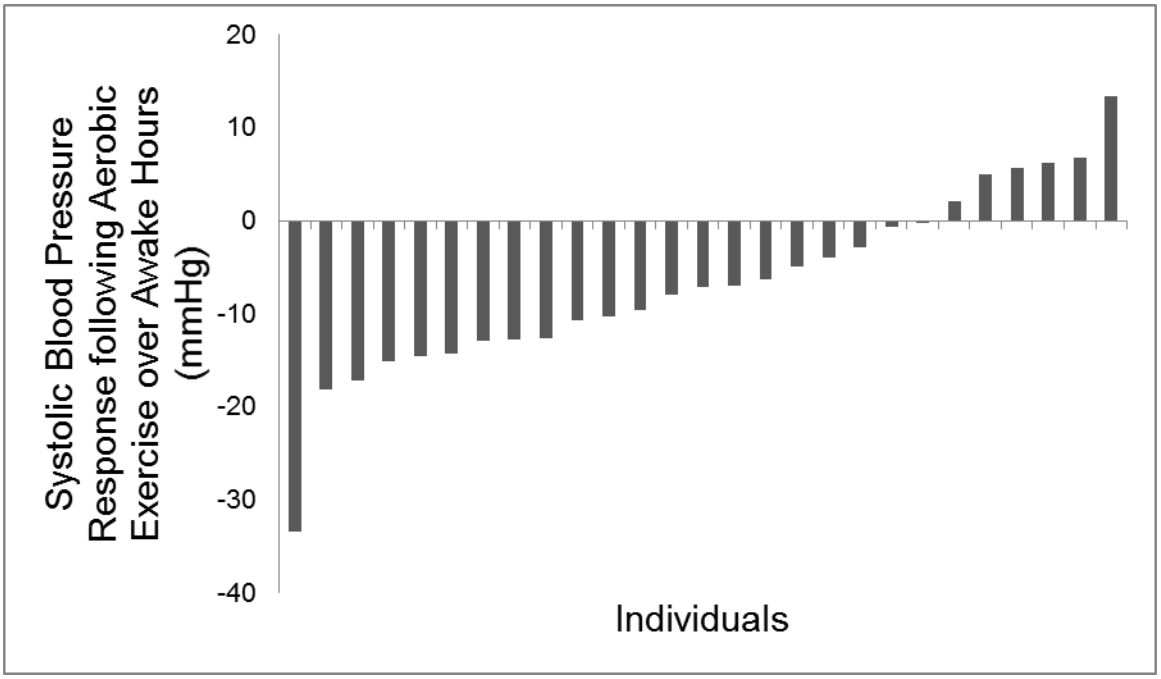
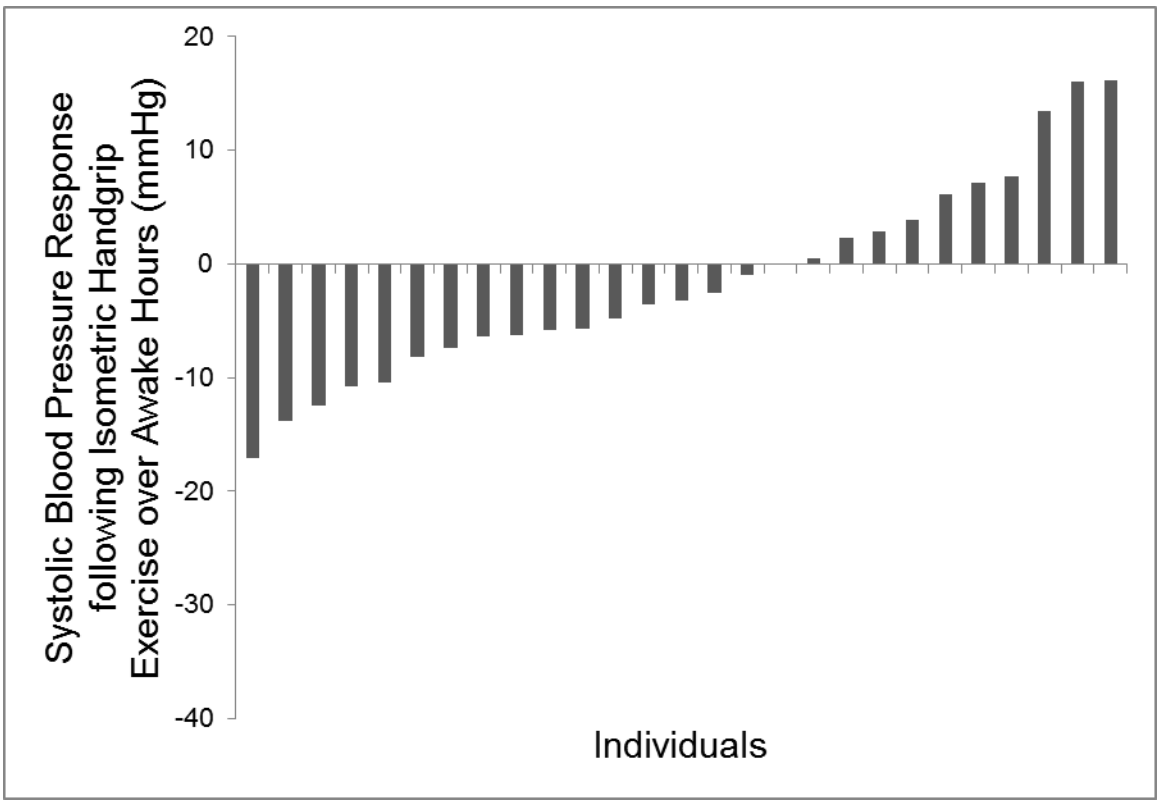


Figure S2


Systolic Blood Pressure Response following Isometric Handgrip Exercise over Awake Hours (mmHg)
20
10
0
-10
-20
-30
-40
Individuals

SUPPLEMENT DATA TABLES

Table S1. Multiple variable regression models identifying clinical correlates of the resting blood pressure response to aerobic exercise training among adults with prehypertension (n=5). Resting blood pressure response to exercise training was defined as average resting blood pressure before training subtracted from average resting blood pressure after training at each hourly interval.

Variable	β (±SE)	*p*
Awake Systolic Blood Pressure		
Pre-training resting systolic blood pressure	-0.863±0.137	<0.01
Pre-training waist circumference	-1.273±0.403	0.03
Awake Diastolic Blood Pressure		
Pre-training diastolic blood pressure	-0.623±0.212	0.01
Pre-training ambulatory arterial stiffness index	-2.633±13.834	0.86
Sleep Systolic Blood Pressure		
Pre-training systolic blood pressure	-1.004±0.160	<0.01
HOMA change following training	10.025±1.793	0.03
Pre-training ambulatory arterial stiffness index	30.223±14.486	0.17
Sleep Diastolic Blood Pressure		
Pre-training diastolic blood pressure	-0.957±0.113	<0.01
Peak oxygen uptake change following training	-3.211±0.680	0.04
Pre-training ambulatory arterial stiffness index	-13.468±8.389	0.25
19 Hour Systolic Blood Pressure		
Pre-training systolic blood pressure	-0.789±0.110	<0.01
HOMA change following training	5.467±1.427	0.03
19 Hour Diastolic Blood Pressure		
Pre-training diastolic blood pressure	-0.757±0.120	<0.01
Pre-training nitrite + nitrate	-0.091±0.029	<0.01
Pre-training ambulatory arterial stiffness index	-9.131±8.745	0.37

HOMA, Homeostatic Model Assessment of Insulin Resistance. Ambulatory arterial stiffness index [1 – (slope of DBP vs SBP over 19 hours]][67] was calculated using the resting control experiment before training (Figure 1). Best fit model is displayed. Non-significant covariates were included if they improve the fit of the model.

Table S2. Multiple variable regression models identifying clinical correlates of the resting blood pressure response to isometric handgrip resistance exercise training among adults with prehypertension (n=5). Resting blood pressure response to exercise training was defined as average resting blood pressure before training subtracted from average resting blood pressure after training at each hourly interval.

Variable	β (±SE)	*p*
Awake Systolic Blood Pressure		
Pre-training systolic blood pressure	-0.702±0.127	<0.01
Pre-training nitrite + nitrate	0.680±0.162	0.05
Pre-training ambulatory arterial stiffness index	-3.894±24.326	0.89
Awake Diastolic Blood Pressure		
Pre-training diastolic blood pressure	-0.925±0.153	<0.01
Pre-training ambulatory arterial stiffness index	-49.109±18.997	0.08
Sleep Systolic Blood Pressure		
Pre-training systolic blood pressure	-0.504±0.165	<0.01
Systolic blood pressure response	0.347±0.136	0.02
Pre-training ambulatory arterial stiffness index	-74.936±22.561	0.05
Sleep Diastolic Blood Pressure		
Pre-training diastolic blood pressure	-0.781±0.131	<0.01
Pre-training ambulatory arterial stiffness index	-24.813±44.508	0.62
19 Hour Systolic Blood Pressure		
Baseline systolic blood pressure	-0.600±0.124	<0.01
Systolic blood pressure response to acute IHG before training	0.211±0.096	0.03
Pre-training nitrite + nitrate	0.454±0.154	0.06
19 Hour Diastolic Blood Pressure		
Baseline diastolic blood pressure	-0.820±0.104	<0.01
Pre-training ambulatory arterial stiffness index	-24.214±22.131	0.35

Ambulatory arterial stiffness index [1 – (slope of DBP vs SBP over 19 hours]][67] was calculated using the resting control experiment before training (Figure 1). Best fit model is displayed. Non-significant covariates were included if they improve the fit of the model.

Table S3. Arterial stiffness parameters (mean±SEM) over 35 and 60 minutes following acute aerobic exercise, isometric handgrip exercise, and non-exercise control before training among adults with prehypertension.

	Aerobic			Isometric Handgrip			Control		
	Baseline	**35 Minutes Post**	**60 Minutes Post**	**Baseline**	**35 Minutes Post**	**60 Minutes Post**	**Baseline**	**35 Minutes Post**	**60 Minutes Post**
Carotid-femoral PWV ($m \cdot s^{-1}$) (n=27, n=23) ‡	8.53±0.22	8.54±0.21	8.43±0.22	8.64±0.23	8.58±0.23	8.34±0.31	8.40±0.21	8.64±0.23	8.64±0.27
Femoral-ankle PWV ($m \cdot s^{-1}$) (n=24) §	10.27±0.28	10.12±0.28	10.37±0.33	10.29±0.26	10.05±0.32	10.50±0.25	10.33±0.24	10.46±0.26	10.58±0.31
Central systolic blood pressure (mmHg) (n=25) ‡	116.6±2.3	115.3±2.2*,†	115.2±2.5*,†	117.4±2.0	121.0±2.6	120.7±2.5	118.2±2.0	121.4±2.4	120.5±2.7

PWV-Pulse Wave Velocity. *p≤0.05 time x condition effect vs control; †p≤0.05 time x condition effect vs isometric handgrip.
‡Carotid-femoral PWV was measured for all 27 subjects at baseline and 35 minutes post. However it was only measured for 23 subjects at 60 minutes post, due to insufficient data quality for the other four subjects at this time point.
§Femoral-ankle PWV was measured for 24 subjects, due to insufficient data quality for the other three subjects.
‡Central systolic blood pressure was measured for 25 subjects, due to insufficient data quality for the other two subjects.

Table S4. Resting arterial stiffness parameters (mean±SEM) before and after aerobic and isometric handgrip resistance exercise training among adults with prehypertension.

	Aerobic Group (n=6)		Isometric Handgrip Group (n=5)	
	Before Training	**After Training**	**Before Training**	**After Training**
Carotid-femoral PWV ($m \cdot s^{-1}$)	8.01±0.46	7.51±0.46*	9.37±0.21†	8.85±0.13
Femoral-ankle PWV ($m \cdot s^{-1}$)	10.98±0.24	11.20±0.35	10.32±0.68	10.03±0.33
Central systolic blood pressure (mmHg)	115.6±3.2	114.2±4.3	118.6±6.1	122.9±3.6

PWV-Pulse Wave Velocity. *p≤0.05 time effect vs pre-training. †p≤0.05 higher than aerobic group at baseline.

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Chapter 3 - Methods

Participants

Sedentary subjects 18 to 55 years old with pre- to Stage 1 hypertension (SBP ≥120 to <160 and/or DBP ≥80 to <100 mmHg) and a body mass index (BMI) ≥25 to <40 $kg \bullet m^{-2}$ were recruited by strategic placement of newspaper advertisements, flyer distribution, direct mailings, email lists, media interviews by the investigators, and local radio station public service announcements throughout Hartford and Tolland Counties. Volunteers were screened by telephone and excluded from further study participation if they were determined to have any of the following: SBP ≥160 mmHg and/or DBP ≥100 mmHg, symptomatic atherosclerotic cardiovascular disease, diabetes mellitus, asthma, thyroid dysfunction, pancreatitis, acute illness, on medication for depression, smoke, drink two or more alcoholic drinks per day, an expressed desire to lose weight as a result of study participation, and physical limitations to perform exercise. Women were pre-menopausal, not pregnant, and regularly menstruating.

Any medications that could potentially influence BP including inhaled or oral steroids, nonsteroidal anti-inflammatory agents, aspirin, antihypertensive and hyperlipidemic medications, nutritional supplements besides one-a-day vitamin, cold medications, hormone-altering contraception, or herbal supplements were stopped at least four weeks before any testing. If subjects were taking antihypertensive medications, they needed to express willingness to discontinue these medications with physician permission throughout the study. Subjects discontinuing antihypertensive medications were monitored for evidence of accelerated hypertension (SBP ≥160 and/or DBP ≥100 mmHg), and if this was observed were excluded from further

participation. Four participants discontinued their antihypertensive medications to participate in the study. Subjects indicated their willingness to participate by signing an informed consent form approved by the University of Connecticut and Hartford Hospital Institutional Review Boards.

Study Procedure

This study was a randomized controlled crossover trial utilizing methods based upon our laboratory's prior work in exercise and hypertension[1-3] (Figure 1). Subjects (n=27) completed an orientation (Visit 1), two graded cardiopulmonary exercise stress tests (GEST, Visits 2 & 3), and assessments of maximum voluntary contraction (MVC), arm volume, and fasting blood sampling and analysis (Visit 3). They next completed three acute exercise (i.e., postexercise hypotension, PEH) experiments in random order (Visits 4 through 6): aerobic exercise (30 minutes cycling at 60% peak oxygen consumption, VO_{2peak}), IHG (4x2 minute bilateral contractions at 30% MVC), and non-exercise control (30 minutes of seated rest). We measured BP and pulse wave velocity (PWV), an index of arterial stiffness, in the laboratory before and for 60 minutes after each experiment. The subject left the laboratory, proceeded with normal activities, and returned the monitor the next morning[1-5].

After completion of the PEH experiments, 11 of the 27 subjects volunteered to participate in an exercise training program to investigate whether aerobic versus IHG resistance exercise training influenced resting BP and/or PEH (Figure 1). These individuals completed a four week wait list control period[6], after which SBP/DBP were not different than before the wait list control period ($p>0.05$). The subjects were then randomly assigned to complete either a supervised aerobic (n=6, 60% VO_{2peak}, 45

minutes per day) or IHG (n=5, 30% MVC, 4x2 minutes bilateral) exercise training program three days per week for eight weeks. During the last week of training, each subject completed a post-training cardiopulmonary GEST (Visit 7, Figure 1). Then, we reassessed PEH (Figure 1, Visits 8 & 9) following the identical protocol of the pre-training PEH experiments, with the intensity of aerobic exercise monitored based upon results of the post-training cardiopulmonary GEST. Visits 7 through 9 were each separated by 48 hours, which was long enough to avoid the confounding effects of PEH from the previous session[7], but short enough to avoid the confounding effects of detraining on BP[8, 9]. Body weight was measured at each study visit to ensure weight maintenance. The female subjects logged their menstrual cycle to ensure that all testing would be performed in the follicular phase (days 1 to 10).

The primary site of all experimental visits and exercise training was the Hartford Hospital Exercise Physiology Laboratory, Hartford, CT. Subjects also had the option to complete visits not including graded exercise stress tests at the University of Connecticut Center for Health, Intervention, and Prevention, Storrs, CT.

Measures

Medical Health Questionnaire (Visit 1)

We administered a medical health questionnaire containing questions regarding medical history, medication use, and lifestyle habits at the orientation visit. Female subjects were issued a menstrual diary which they maintained and reviewed with study investigators at each visit.

Physical Activity Questionnaire (Visit 1)

We administered the Paffenbarger physical activity questionnaire[10] at the

orientation visit to ensure the subjects met the study inclusion criteria of being sedentary to physically inactive defined as exercising less than two times per week during the past two months. This questionnaire was developed and validated to assess habitual leisure time physical activity levels among adult populations[10, 11].

Anthropometric Measurements (Visit 1)

We measured body weight and height using a calibrated balance beam scale at the orientation visit to calculate BMI. Waist circumference was measured at the umbilicus using a non-distensible Guilick tape measure. Weight was assessed on a weekly basis throughout the study to ensure weight maintenance, defined as ±2.25 kg (5.0 lb) of orientation weight.

Auscultatory Blood Pressure Measurement (All Visits)

A trained investigator (GIA) measured resting BP in the laboratory according to the standards set by the American Heart Association[5] using an automated BPTRU monitor (BPTRU Medical Devices; Coquitlam, Canada). At the orientation visit subjects sat for five minutes after which BP was measured three times, one minute apart in each arm and averaged. Up to three additional readings were taken if necessary until three readings in each arm in agreement to within 5 mmHg were obtained. During experimental visits BP was measured continuously every two minutes in the non-dominant arm.

Ambulatory Blood Pressure Monitoring (All Visits)

A trained investigator (GIA) performed all ambulatory BP assessments for the study. Subjects wore the same Oscar2 automatic noninvasive ambulatory BP monitor (Suntech Medical Instruments Inc., Raleigh, NC) on the nondominant arm after each of

the nine study visits, of which the purpose of the first three was to determine BP status and familiarize them with wearing the unit[4, 12, 13]. A calibration check was done with a mercury sphygmomanometer using a t-tubule upon attachment of the ambulatory BP monitor to the subject. The ambulatory BP monitor was programmed to record BP at regular intervals three times per waking hour and two times per sleeping hour. The monitor obtained a second reading if consecutive readings differ by >50 mmHg for SBP, >40 mmHg for DBP, or >50 mmHg for pulse pressure. Subjects were instructed to leave the laboratory and proceed with normal activities, not to exercise, and when each ambulatory BP measurement was being taken to keep their arm still and extended at their side. The next morning they detached the monitor and physically returned it that day to the study investigators at either Hartford Hospital or the University of Connecticut. Subjects carried a standard journal, recording activities performed during each measurement, any unusual physical or emotional events, and sleep and wake times. We omitted ambulatory BP readings of SBP >220 or <80 mmHg, or DBP >130 or <40 mmHg according to the manufacturer's exclusion criteria. Computerized ambulatory BP reports were acceptable if at least 80% of the potential BP readings were obtained. Nocturnal BP dipper status (SBP and DBP fall ≥10% of daytime values)[14] and ambulatory arterial stiffness index [1 – (slope of DBP vs SBP over 19 hours]][15] were calculated using the resting control experiment before training (Figure 1).

Arterial Stiffness Assessment (Visits 4, 5, 6, 8, & 9)

A trained investigator (GIA) measured carotid-femoral PWV, an index of central arterial stiffness; femoral-ankle PWV, an index of peripheral arterial stiffness; and central SBP using the SphygmoCor® CPV Central Blood Pressure/Pulse Wave Velocity

System (AtCor Medical; Sydney, Australia) according to standards set by the European Society of Cardiology[16]. Doppler waveforms at the carotid, femoral, and dorsalis-pedis arteries on the non-dominant side were assessed with a Millar tonometer. The average time difference between the Doppler waveforms and simultaneous electrocardiogram tracings was calculated over 10 seconds to determine pulse transit time. Carotid-femoral pulse transit distance (from femoral pulse to sternal notch via the umbilicus minus the distance from carotid pulse to sternal notch) and femoral-ankle pulse transit distance (from femoral pulse to dorsalis pedis pulse) were divided by average pulse transit time to calculate central and peripheral PWV, respectively. Finally, central SBP was assessed by analysis of the radial pulse waveform transformed to the aortic pulse waveform using a generalized transfer function[16]. We rejected and immediately repeated any measurements with a heart rate difference of more than five beats per minute between readings, pulse transit time standard deviation ≥6% of the mean value, and/or radial pulse waveform operator index <80 according to the manufacturer's exclusion criteria[16]. The day-to-day coefficient of variation was 5.3% for carotid-femoral PWV, 8.3% for femoral-ankle PWV, and 3.2% for central SBP.

Graded Exercise Stress Test (Visit 2)

The initial maximal graded exercise stress test (GEST) on a treadmill was performed at Hartford Hospital to exclude atherosclerotic ischemic heart disease. The GEST employed the Bruce protocol[17]. Subjects were monitored by a 12-lead ECG system with BP and heart rate measurements taken periodically before, during, and after the GEST. A clinical cardiologist performed a brief physical examination on the subject immediately before the GEST to determine the subject's clinical status. The

cardiologist then remained present for the GEST to monitor the subjects' ECG and physical signs. Upon completion of the GEST, the medical cardiologist reviewed the ECG for signs of ischemia. No subjects were found to have ischemic ECG changes.

Cardiopulmonary Graded Exercise Stress Test (Visits 3 & 7)

At the start of the study and during the last week of training, subjects performed a cardiopulmonary GEST on a cycle ergometer (Monarch 839E Digital Cycle Ergometer, Stockholm, Sweden) at Hartford Hospital. Subjects cycled continuously at a constant cadence of 60 revolutions per minute with the resistance increased by 0.5 kiloponds (30 watts) every two minutes until volitional exhaustion. Investigators used breath-by-breath analysis of expired gases (ParvoMedicsTrueOne® 2400 Metabolic Measurement System, ParvoMedics Inc., Sandy, UT) to determine VO_{2peak}. Heart rate was measured each minute and BP was measured by auscultation 30 seconds prior to the conclusion of each two minute incremental stage. The pre-training GEST results (Visit 3) were used to calculate the intensity of the aerobic exercise PEH experiment before training and aerobic exercise training sessions (Figure 1) from a linear regression plot of work rate and heart rate as a function of VO_2 [17]. Meanwhile the post-training GEST results (Visit 7) were used to calculate the intensity of the aerobic exercise PEH experiment after training (Figure 1).

Volumetric Arm Measurement (Visits 3 & 7)

At the start of the study and during the last week of training, a trained investigator (GIA) measured arm volume. Subjects immersed one arm in a water displacement arm volumeter containing warm water[18]. The displaced water was collected into a volumetric jug. The water volume in the jug was measured, giving the arm volume. The

procedure was repeated for each arm.

Blood Sampling and Analysis (Visits 3 & 7)

Fasting blood samples were drawn without stasis from an antecubital vein using an indwelling catheter into red (no additive) and purple (potassium EDTA) top tubes. Blood samples were then centrifuged at 2500g and 23 °C for 15 minutes. Serum samples were transferred from red top tubes and plasma samples from purple top tubes into 1.8 mL non-pyrogenic storage tubes and frozen at -80 °C until analysis. Serum high density lipoprotein cholesterol, total cholesterol, triglycerides, glucose, and insulin were determined by colorimetric enzymatic assays (Quest Diagnostics, Wallingford, CT). Low density lipoprotein cholesterol was calculated with the Friedwald equation[19]. The homeostatic model assessment [HOMA, glucose ($mmol \cdot L^{-1}$) x insulin ($pmol \cdot L^{-1}$) x 156.3^{-1}] was calculated as a measure of insulin sensitivity[20]. Serum nitric oxide (NO) metabolites including nitrite (NO_2^-) and nitrate (NO_3^-) levels were measured by colorimetric enzymatic assays (R&D Systems, Minneapolis, MN). All samples were run on a single assay by a trained investigator (KDB) with sensitivity 0.25 $\mu mol \cdot L^{-1}$ and coefficient of variation 9.1%[21].

Acute Exercise Experiments (Visits 4 through 6)

To measure PEH before exercise training, subjects completed three blinded experiments in random order at least 48 hours apart (Figure 1). All experiments for each subject began at the same time of day. Start times between subjects ranged from 0500 and 1100 hours depending on the subject's schedule. All female subjects completed all experiments during the follicular phase (days 1 to 10) of the menstrual cycle, as verified by diary recording. Subjects were instructed to consume a standard

breakfast two to three hours before all experiments consisting of 250 mL orange juice, 125 mL skim or 1% milk, and either 125 mL of plain cereal such as cornflakes, two slices white toast, one English muffin, or one bagel 9 cm in diameter. They were also instructed to refrain from caffeine beverages for six hours before all experiments.

All experiments began with 10 minutes of supine rest, supine assessment of PWV, and then 20 minutes of seated rest with BP measured every 2 minutes. This was followed by one of three experiments in random blinded order (www.randomization.com) that consisted of: 1) Aerobic Exercise- cycling for 20 minutes at 60% VO_{2peak} with a five minute warm up and cool down to total 30 minutes. Intensity was monitored using a Polar Heart Rate Monitor (Lake Success, NY) based upon a linear regression plot of work and heart rate versus VO_2 achieved on the cardiopulmonary GEST; 2) IHG Resistance Exercise- a digital handgrip device (Zonaplus, Boise, ID) was held while sitting upright in a chair with feet flat on the floor, and a single maximal contraction of the hand flexor muscles with each hand was completed to determine MVC. Subjects then performed four, two minute alternating bilateral contractions of the hand flexor muscles at 30% MVC with one minute rest between contractions[22, 23]. Subjects were provided feedback and encouragement to sustain 30% MVC. The percentage of time they held this tension was registered by the digital device and averaged 85.1±1.5%; and 3) Non-Exercise Control- sitting quietly for 30 minutes. All experiments concluded with 30 minutes of seated recovery followed by 30 minutes of supine recovery, with BP measured every 2 minutes and PWV measured 35 and 60 minutes into the recovery period. Subjects left the laboratory wearing the same ambulatory BP monitor as they wore during the screening Visits 1 through 3 until

the next morning.

Supervised Exercise Training Program

Subjects volunteering for the exercise training addendum (n=11) first participated in a four week wait list control period[6], after which SBP/DBP were not different than before the wait list control period ($p>0.05$). The purpose of the wait list control period was to isolate the effects of exercise from the BP changes occurring over time due to possible extraneous factors unrelated to exercise such as seasonal variation[24] and psychosocial stressors[25].

The subjects were then randomly assigned to complete supervised aerobic exercise (n=6) or IHG (n=5) training. Subjects assigned to the aerobic exercise group cycled at each session on a Monark 893E Digital Cycle Ergometer (Monark Inc., Stockholm, Sweden) at 40% to 70% VO_{2peak} using their percent of heart rate reserve range determined from the cardiopulmonary GEST to regulate exercise intensity[17]. The duration of each exercise session progressively increased from 15 to 40 minutes during the first four weeks of training. Once subjects were able to perform 40 minutes of exercise, they continued this amount of exercise three days per week for an additional four weeks, totaling eight weeks of participation. The intensity of exercise was 40% to 60% VO_{2peak} during the first four weeks of training and 60% to 70% during the second four weeks. An additional five minute warm-up and cool-down period was included so that each session totaled 25 to 50 minutes. During exercise, heart rate from a Polar heart rate monitor was recorded onto standardized forms at five minute intervals, and the Borg Rating of Perceived Exertion on the 6 to 20 scale[26] was recorded halfway through the session[17].

Subjects assigned to the IHG group began each session sitting upright in a chair with feet flat on the floor. They performed an assessment of MVC followed by four, two minute alternating bilateral contractions of the hand flexor muscles at 30% MVC with one minute rest between contractions as in the acute IHG experiments. Once during each of the second and fourth contractions, heart rate from a Polar heart rate monitor, and the Borg Rating of Perceived Exertion on the 6 to 20 scale[26] was recorded onto standardized forms[17].

Timeline Followback for Exercise (TLFB-E)

The Timeline Followback for Exercise (TLFB-E) is a self-report calendar diary method used in clinical and research settings to assess daily exercise habits over a specified time through an interview style approach[27, 28]. Subjects completed the TLFB-E after the wait list control period before starting exercise training, for the recording of exercise habits over the past four weeks. The TLFB-E was also completed weekly during the eight week supervised exercise training program. These TLFB-E recordings confirmed that subjects were sedentary during the wait list control period and did not engage in exercise outside of supervised sessions with research personnel during the exercise training period.

The TLFB-E represents a traditional monthly calendar in which study subjects record the *frequency*, *intensity, time,* and *type* (FITT) of the exercise they perform over a specified time frame. *Frequency* was recorded as the number of bouts completed, *intensity* of each exercise bout was recorded with the Borg Rating of Perceived Exertion on the 6 to 20 scale[26], *time* was recorded as minutes per bout, and *type* was recorded as the modality of the exercise bout and categorized as aerobic, resistance, flexibility, or

a combination of exercise modalities.

Statistical Analysis

Data are reported as mean ± standard error. Repeated measures analysis of covariance (RMANCOVA) compared BP over hourly intervals between experiments (control, aerobic, and IHG) and before versus after training with age and BMI as covariates over awake (1 to 10 hours post-exercise), sleep (11 to 19 hours), and 19 hours. PEH was calculated before and after training as the BP change following control versus the BP change following exercise (aerobic and IHG) at hourly intervals. The resting BP response to exercise training was calculated as ambulatory BP over awake, sleep, and 19 hours on the day of the resting control experiment before versus after training at hourly intervals.

RMANCOVA compared arterial stiffness dependent variables (carotid-femoral PWV, femoral-ankle PWV, and central SBP) over time (baseline, 35 minutes, and 60 minutes post-exercise) between experimental conditions (control, aerobic, and IHG) and before versus after training with age and BMI as covariates. The arterial stiffness response to acute exercise was calculated as the arterial stiffness change following control versus the arterial stiffness change following exercise. The resting arterial stiffness response to exercise training was calculated as the average pre-exercise baseline value across the acute experimental sessions before (Visits 4 through 6, Figure 1) versus after training (Visits 8 & 9, Figure 1).

Multiple variable linear regression examined clinical correlates of PEH and the resting BP response to exercise training. Independent variables included baseline PWV and PWV change from baseline in order to examine the correlation between BP and

central arterial stiffness changes before and after acute and chronic aerobic and IHG resistance exercise. We also included other independent variables based upon clinical correlates of PEH and BP response to exercise training identified in previous studies by ourselves[29-33] and others[34, 35]: nocturnal BP dipper status, age, VO_2peak, baseline BP, peak SBP change to a GEST, HOMA, NO metabolites, and waist circumference.

We established minimum statistical power β=80% and significance α=0.05. Based upon previous literature, we expected SBP reductions of 6.9±1.1 mmHg[36] and 13.4±1.1 mmHg[37] following aerobic and IHG exercise respectively, requiring n=24 subjects to test the hypothesis that PEH magnitude would differ by modality. To detect clinical correlates of PEH, based on our previous work[29], we expected r^2=0.30 attributed to two significant independent variables and r^2=0.20 attributed to eight other independent variables, requiring n=22 subjects to detect clinical correlates. Thus, a sample size of 27 subjects was adequately powered to compare PEH by modality as well as assess clinical correlates of PEH, although the sample size for the training groups (aerobic n=6, IHG n=5, Figure 1) was not. However, power among the training groups was increased by employing mixed linear models with hourly intervals as an alternative to RMANCOVA; thus representing each subject as 19 hourly BP measurements and making the effective sample size n=5x19=95. All statistical analyses utilized SPSS 14.0 (Chicago, IL) except for mixed linear models (SAS 9.3, Cary, NC) and power calculations (SAS 9.3 and PASS 2008, NCSS, Kaysville, UT).

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Chapter 4 – Discussion

The purpose of this dissertation was to compare the blood pressure (BP) and arterial stiffness responses to acute and chronic aerobic and isometric handgrip (IHG) resistance exercise among adults with high BP, and examine if changes in arterial stiffness account for some of the variability in the BP response following acute and chronic aerobic and IHG resistance exercise. To achieve this purpose, we compared the BP and arterial stiffness responses to acute aerobic and IHG resistance exercise among young and middle-aged adults with pre- to established hypertension in a randomized cross over design. In a subset of these people, we also examined changes in resting BP and resting arterial stiffness after eight weeks of either aerobic or IHG resistance exercise training. This chapter serves as a synthesis and conclusion of the findings. It will be organized first by discussing the specific aims and hypotheses along with relevant findings. Then, the significance of the findings as related to the current literature will be explored by discussing the antihypertensive benefits of aerobic versus IHG resistance exercise, and arterial stiffness changes as a potential mechanism for differences in the antihypertensive effects of exercise by modality. Finally, future research pertaining to the findings will be discussed.

Specific Aims, Hypotheses, and Relevant Findings

Specific Aim 1: To examine the BP lowering effects of acute and chronic aerobic exercise compared to acute and chronic IHG resistance exercise among adults with high BP.

Hypothesis 1: We hypothesized that BP would be lowered to greater levels following IHG resistance exercise than aerobic exercise, with respect to both acute exercise and

exercise training. Our major finding was acute aerobic exercise lowered BP 5 to 7 mmHg after acute and chronic aerobic exercise, while BP was not different after acute IHG resistance exercise, and became 5 to 7 mmHg higher after than before IHG training compared to control. Contrary to our hypothesis, acute and chronic IHG resistance exercise were not superior to acute and chronic aerobic exercise in lowering ambulatory BP over 19 hours. In fact, BP was 4 to 5 mmHg lower after than before acute aerobic versus IHG exercise, and resting BP was 6 to 11 mmHg lower after versus before aerobic versus IHG exercise training. Our findings are in agreement with two reports that acute[1] and chronic[2] IHG resistance exercise did not lower BP, while they are in contrast with others that concluded acute and chronic IHG resistance exercise reduced BP to the same or greater levels as acute[3] and chronic[4-8] aerobic exercise.

Specific Aim 2: To examine central arterial stiffness changes before and after acute and chronic aerobic exercise and IHG exercise among adults with high BP.

Hypothesis 2: We hypothesized that carotid-femoral pulse wave velocity (PWV), an index of central arterial stiffness, would be lowered to greater levels following IHG resistance exercise than aerobic exercise, with respect to both acute exercise and exercise training. Contrary to our hypothesis, the arterial stiffness responses to acute (Table S3) and chronic exercise (Table S4) did not differ by modality. Carotid-femoral PWV was not different after acute aerobic or IHG resistance exercise, but was 0.5 $m \cdot s^{-1}$ lower after aerobic exercise training with a similar non-significant trend after IHG resistance exercise training (Table S4). Our findings regarding the arterial stiffness response to aerobic exercise agree with previous reports: central arterial stiffness

among adults with high BP did not change following acute aerobic exercise[9-11], but decreased following aerobic exercise training in a meta-analysis of 610 subjects from 15 studies (d_+= -0.88, p<0.01)[12]. No prior study to our knowledge has tested the acute or chronic arterial stiffness responses to IHG resistance exercise.

Specific Aim 3: To examine the correlation between BP and central arterial stiffness changes before and after acute and chronic aerobic and IHG resistance exercise among adults with high BP.

Hypothesis 3: Changes in carotid-femoral PWV after versus before aerobic and IHG resistance exercise will correlate with changes in BP after versus before aerobic exercise and IHG resistance exercise, with respect to both acute exercise and exercise training. Contrary to our hypothesis, changes in arterial stiffness and BP were not correlated (p>0.05). Furthermore, the arterial stiffness responses to acute (Table S3) and chronic exercise (Table S4) did not differ by modality, in contrast to the differences we observed in BP (Figures 2, 4). In sum, our data did not support reductions in central arterial stiffness as a mechanism for the greater antihypertensive effects of aerobic versus IHG resistance exercise.

Impact of the Findings on the Current Literature

Previous Studies of the Blood Pressure (BP) Response to Isometric Handgrip Exercise (IHG)

Several randomized controlled trials have indicated the BP reductions that result from acute[3] and chronic[4-8] IHG resistance exercise appear to be equal to or even greater than those that result from aerobic exercise. Discrepancies between our study

and these other reports[3-8] may be partially attributed to differences in study design. Strengths of our study were that it was the first randomized crossover trial examining PEH following IHG resistance versus aerobic exercise compared to control among the same individuals with high BP. Furthermore, our study sample was over twice the size of previous studies examining the antihypertensive effects of acute IHG[3-8]. Therefore, the unique features of our randomized controlled trial in which subjects served as their own control have influenced the difference in outcomes. In sum, the positive findings of previous studies[3-8] regarding antihypertensive benefits of IHG may be due to their less rigorous scientific designs than our study.

In further support of this interpretation, the only other study examining the antihypertensive effects of IHG exercise with ambulatory BP monitors, Stiller-Moldovan et al found ambulatory BP was not different after versus before IHG training[2]. All reports except one[1] that found BP was lowered after acute[3] and chronic[4-8] IHG measured auscultatory BP in the laboratory. However, our findings (Figures 2, 4) along with those of Stiller-Moldovan et al[2] indicate antihypertensive effects of IHG observed in the laboratory[3-8] may not persist under ambulatory conditions of daily living[2, 13]. This difference in findings may highlight the importance of using ambulatory BP monitoring, the gold standard clinical method for assessing BP. Its major strengths include that it assesses circadian BP patterns, and predicts cardiovascular outcomes and target organ damage more robustly than office or laboratory measurements[13].

Aside from differences in study design, it is also noteworthy that previous studies differed from ours in the study populations that were examined[1-8]. Subjects from studies reporting antihypertensive benefit from IHG had either normal BP[3, 4, 8] or BP controlled

to normal levels with antihypertensive medication[4, 5, 7]. They were also normal weight[3-8], physically active[3, 4], of average cardiorespiratory fitness[3, 4], and likely Caucasian based upon geographic location although race was not reported[3-8]. By contrast, subjects from our study were in the early stages of hypertension, not receiving antihypertensive medication, sedentary, obese, low cardiorespiratory fitness, and majority (56%) African Americans (Table 1). These differences in the study population demographics could be another factor contributing to discrepancies between studies regarding BP outcomes following IHG resistance exercise. The American Heart Association[14] previously cautioned that only limited populations have been evaluated to date[1-8] regarding the antihypertensive efficacy of IHG resistance exercise. Our findings reinforce this caution, for we found IHG on average did not reduce BP among young adults in the early stages of high BP, a critical demographic for targeted therapeutic intervention to prevent and delay the progression of hypertension[14, 15].

Inter-Individual Variability of Blood Pressure (BP) Response to Exercise

Besides the variability between studies described above, a growing body of evidence indicates that health outcomes following exercise exhibit variability among individuals that is belied by mean results[16, 17]. For example, the standard deviation of the change in a variety of cardiovascular disease risk factors following aerobic exercise training in the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) study (n=723)[18] exceeded the mean value of the change that included BP. In a recent meta-analysis of randomized controlled trials of the BP change following IHG resistance exercise training[19], the standard deviation also exceeded the mean value of the change. We also found the standard deviation of the BP change following acute aerobic (-

6.8±9.8 mmHg, Figure S1) and acute IHG exercise (-1.6±8.8 mmHg, Figure S2) exceeded the mean value of the change. Furthermore, 10 of the 27 participants in our study did not achieve clinically significant antihypertensive benefit [systolic (SBP) and diastolic blood pressure (DBP) reduced by ≥2 mmHg] following acute aerobic exercise (Figure S1); while 13 did achieve such benefit following IHG (Figure S2). Nonetheless, ambulatory BP was on average 5 mmHg lower after acute aerobic than acute IHG exercise. In addition, most of the participants (i.e., 85%) individually experienced a greater BP reduction following acute aerobic than acute IHG exercise, reinforcing our major finding that acute aerobic was superior to acute IHG exercise in lowering ambulatory BP throughout the day time hours.

Mechanisms for the Blood Pressure (BP) Response to Exercise

Ohm's law states that BP is equal to the product of cardiac output (Q) and TPR[20]. Our laboratory and others have observed unchanged[21] or increased Q[22-24] following acute aerobic exercise by healthy individuals, suggesting PEH appears to be primarily the result of decreased TPR. A physiological change which could increase vessel radius thus decreasing TPR and lowering BP, following both acute and chronic aerobic exercise is reduced central arterial stiffness.

The secondary aim of our study therefore was to investigate arterial stiffness changes as a potential mechanism for differences in the antihypertensive effects of exercise by modality. Elevated central arterial stiffness is an independent cardiovascular disease risk factor[25-28] that is also implicated in the etiology of hypertension[29, 30]. Among adults with high BP, previous reports indicated central arterial stiffness did not change following acute aerobic exercise[9-11], but decreased following

aerobic exercise training in a meta-analysis of 610 subjects from 15 studies (d_+= -0.88, p<0.01)[12]. Similarly we found carotid-femoral PWV, an index of central arterial stiffness, was not different after acute aerobic exercise (Table S3) but was 0.5 $m \cdot s^{-1}$ lower after aerobic exercise training (Table S4). There were no differences in arterial stiffness response to acute (Table S3) or chronic exercise (Table S4) by modality, in contrast to the differences we observed in BP (Figures 2, 4). In addition, changes in arterial stiffness and BP were not correlated (p>0.05, data not shown). In sum, the data do not support reductions in central arterial stiffness as a mechanism for the greater antihypertensive effects of aerobic versus IHG resistance exercise.

However, the present study only measured BP and arterial stiffness after acute exercise and eight weeks of exercise training, without obtaining data after longer-term exercise training. Previous reports indicate that functional adaptations (ie, reduced BP[31], increased endothelium-mediated vasodilation[32, 33]) occur early in exercise training, i.e., following acute exercise and up to two weeks of exercise training[31-33]. On the other hand structural changes (e.g., reduced arterial stiffness[31], increased arterial diameter[32, 33], reduced arterial wall thickness[34]) occur later in the training process[31-34]. This difference in the time course of functional versus structural changes could have contributed to the lack of correlation between BP and arterial stiffness changes in our study. Nonetheless, over longer-term exercise training (i.e., >10 weeks), it is possible that structural adaptations including reduced arterial stiffness would stabilize and contribute to BP changes. In support of this supposition, Huang et al's meta-analysis[12] (n=610, k=15) reported that arterial stiffness was reduced to greater levels when subjects performed aerobic exercise training for a greater number of weeks [four to

eight weeks, d_+= -0.35 (95% CI -0.68, -0.02); nine to 16 weeks d_+= -0.69 (-1.13, -0.25); 16 to 26 weeks, d_+= -1.19 (-1.92, -0.47)]. These results indicate that arterial stiffness reductions from aerobic exercise training do not stabilize within relatively short-term exercise training (i.e., eight weeks) such as the present study.

Therefore, it is likely other mechanisms accounted for the greater antihypertensive effects of aerobic versus IHG resistance exercise we observed. Acute aerobic and IHG resistance exercise both increase central sympathetic nerve activity (SNA) during exercise through mechanical and chemical stimulation of afferent muscle neurons[35-40]. However acute aerobic exercise has been widely demonstrated to promote accumulation of muscle metabolites (ATP, potassium ions, hydrogen ions) and release of vasodilators from the endothelium (nitric oxide, prostaglandins), which all reduce alpha-adrenergic responsiveness and increase vascular conductance during and after exercise[35-37]. These changes, termed *functional sympatholysis*, are specific to exercising muscles and therefore occur systemically following aerobic but not IHG resistance exercise. For instance, increased blood flow occurs in both the legs and arms following aerobic cycling[41], but only within the active and not the inactive arm following unilateral IHG resistance exercise[42]. In fact, IHG elicits “open-loop” feedback in which vasoconstriction elicited by mechanical and chemical stimulation of afferent muscle neurons, mechanical torsion of isometrically contracting muscles, and subsequent reductions in blood flow and vascular shear stress promote increased BP[43-48]. Furthermore this response is augmented among individuals with high BP[38-40]. Therefore, this literature is consistent with our findings that aerobic exercise is superior antihypertensive lifestyle therapy than IHG resistance exercise.

The correlation of PEH following aerobic exercise with nocturnal BP dipper status and peak SBP change to a graded exercise stress test (Table 3) further supports the above explanation. For, dipper status associates with nocturnal decline in SNA[49, 50]. Dipper status also associates with renin-angiotensin system activity[49, 51, 52], which has been demonstrated to influence functional sympatholysis by upregulating superoxide[35-37]. Finally, peak SBP change during exercise associates with functional sympatholysis and the extent to which it mitigates increased sympathetic drive during exercise to defend BP[35-37].

Finally, since BP was not different following acute IHG versus non-exercise control (Figure 2), but 5 to 7 mmHg higher following IHG training versus pre-training (Figure 4) different mechanisms may govern the acute versus chronic BP response to IHG. One mechanism which does differ between acute and chronic regulation of BP is pain sensation[53]. Acute pain raises SNA which increases BP, but the associated baroreceptor stimulation acutely reduces pain sensitivity due to transiently increasing endogenous opioids. An intervention like IHG that induces discomfort[54] could acutely reduce BP sensitivity to the painful sensations experienced under normal ambulatory conditions of daily living on the day following a single session. This benefit might partially counteract the unfavorable influence of IHG upon SNA and BP described above[38-40]. On the other hand, when such bouts of acute pain are repeated as in IHG exercise training the effect can be reversed due to dysfunction of the release of opioids leading to a reduction in their analgesic effect[53]. This may explain the increased ambulatory BP following IHG training (Figure 4). Our study cannot be used to test this supposition, as we did not measure biomarkers associated with pain sensation.

In sum, the greater antihypertensive effects of aerobic exercise versus IHG after acute exercise and relatively short-term exercise training did not relate to changes in arterial stiffness but non-structural, functional factors including vascular reactivity and endothelium-mediated vasodilation. These findings are in agreement with the hypothesis formed from previous reports that functional adaptations occur early in exercise training whereas structural changes occur later in the training process[31-34].

Strengths and Limitations

Although this study bore methodological strengths including a randomized controlled crossover design and the clinical gold standard assessment of ambulatory BP [55], it was not without limitations. We were adequately powered to compare the antihypertensive effects of acute aerobic versus IHG resistance exercise and furthermore assess its relationship with central arterial stiffness. Yet, the subpopulations completing the aerobic (n=6) and IHG resistance exercise training (n=5) portion of our study were underpowered so that these findings should be treated with caution.

Another limitation is that variability in the BP response to exercise can be partially attributable to technical error related to obtaining repeated measurements[18]. However we took considerable care to minimize technical error by having all BP assessments performed by a single investigator (GIA) at the same time of day using the same ambulatory BP monitor for the same subject throughout study duration. As a result, the coefficients of variation for baseline SBP/DBP before the acute experiments for a given subject was 2.9%/3.5%, respectively. Thus, technical error did not appear to be a

predominant factor influencing variability in the BP response to exercise among our participants.

Future Research

This dissertation compared the BP responses to aerobic and IHG following acute exercise and eight weeks of exercise training, as well as the correlation between BP and central arterial stiffness changes over these time frames. However, our results over eight weeks of training cannot necessarily be generalized to a longer time period. First, previous reports indicated that functional adaptations to aerobic exercise training follow a different time course than structural adaptations over the first eight weeks of training, but both may stabilize after a longer duration of training[31-34]. Secondly, other factors irrelevant to a shorter exercise training intervention could contribute to BP changes over a longer training intervention (e.g., biological aging, long-term cardiac and vascular remodeling resulting from hypertension). Therefore, future studies should compare the BP and arterial stiffness responses to aerobic exercise training interventions of longer duration (e.g., 52 weeks) to determine whether the results of the present study can be generalized to this longer time period. However, it is likely that any influence of arterial stiffness response upon BP response to exercise is secondary to the widely demonstrated influence of functional sympatholysis[35-37].

Also, this dissertation compared the BP responses to aerobic and IHG resistance exercise but did not address combined aerobic and IHG resistance exercise. It is noteworthy that although acute IHG resistance exercise did not reduce BP on average (Figure 2) and 23 of the 27 participants (85%) individually reduced BP to a greater

extent following acute aerobic than IHG resistance exercise, 13 of the 27 participants (48%) individually reduced BP to a clinically significant degree (SBP and DBP reduced by ≥2 mmHg) below control levels following IHG resistance exercise (Figure S2). Thus, some individuals may gain antihypertensive benefit from IHG and it is possible this benefit occurs additively with the antihypertensive benefits of aerobic exercise. Supporting this possibility, Polito and Farinatti[56] reported that antihypertensive benefit of acute dynamic resistance exercise correlated positively with the involved muscle mass and exercise volume. Although IHG is not high volume exercise in itself, it could be combined with aerobic exercise, which would serve to engage the hand flexor muscles thus increasing the muscle mass involved compared with aerobic exercise only. Therefore, combined aerobic and IHG exercise could hypothetically achieve antihypertensive benefits superior to aerobic exercise only. A further study of the BP responses to acute and chronic combined aerobic and IHG resistance exercise would be required to test this supposition.

Conclusion

Our findings support the recommendations of the American College of Sports Medicine[57], American Heart Association[14], European Society of Hypertension[58], and Canadian Society of Hypertension[59] that aerobic exercise should be the primary modality of choice among adults with high BP for its immediate and sustained BP lowering effects. The present study and eight previous randomized controlled trials[1-8] have evaluated the antihypertensive efficacy of IHG as an alternative exercise modality for this population. Most of these trials have indicated that the BP reductions that result

from acute[3] and chronic[4-8] IHG resistance exercise appear to be equal to or even greater than those that result from aerobic exercise. However, these findings may be a consequence of less scientifically rigorous study designs compared with our study, as well as assessment of BP in the laboratory but not under ambulatory conditions of daily living[3-8]. Therefore, caution is warranted at this time regarding the efficacy of acute and chronic IHG resistance exercise as antihypertensive therapy, considering the results of our randomized controlled crossover trial that IHG yielded less antihypertensive benefit than aerobic exercise for almost all our participants. Aerobic exercise should remain the primary exercise modality to prevent, treat, and control hypertension.

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