

THE EFFECTS OF HIGH INTENSITY INTERVAL TRAINING ON RESTING MEAN
ARTERIAL PRESSURE AND C-REACTIVE PROTEIN CONTENT IN PREHYPERTENSIVE
SUBJECTS

by

BENJAMIN C SKUTNIK

B.A., Luther College, 2008

A THESIS

submitted in partial fulfillment of the requirements for the degree

MASTER OF SCIENCE

Department of Kinesiology
College of Arts and Sciences

KANSAS STATE UNIVERSITY
Manhattan, Kansas

2013

Approved by:

Major Professor
Craig A Harms, PhD

Copyright

BENJAMIN C SKUTNIK

2012

Abstract

Subjects with prehypertension are at risk for developing hypertension (HTN). Hypertension is associated with low-grade systemic inflammation (LGSi). Aerobic exercise training (ET) is a proven means to reduce both blood pressure and LGSi in healthy and diseased subjects. Recently, high intensity interval training (HIIT) has been shown to elicit similar cardiovascular and metabolic adaptations as ET in healthy and at-risk populations in a more time efficient manner. Therefore, we hypothesized that HIIT would elicit greater reductions in blood pressure and LGSi than ET. Twelve pre-hypertensive subjects (systolic blood pressure 127.0 ± 8.5 mmHg; diastolic blood pressure 86.2 ± 4.1 mmHg) were randomly assigned to an ET group (n=5) and a HIIT group (n=7). All subjects performed an incremental test to exhaustion (VO_{2max}) on a cycle ergometer prior to, after 4 weeks, and after 8 weeks of training. Resting heart rate and blood pressure were measured prior to and three times a week during training. LGSi was measured via high-sensitivity C-reactive protein (hs-CRP) prior to, after 4 weeks and after 8 weeks of training. ET subjects performed an eight week exercise training program at 40% VO_2 reserve determined from the VO_{2max} test, while HIIT subjects performed exercise at 60% peak power determined from the VO_{2max} test. ET group trained four days/week while HIIT trained three days/week. ET exercised for 30 minutes continuously at a constant workload and cadence of 60 rpm while HIIT performed a protocol on a 1:1 work-to-rest ratio at a constant workload and cadence of 100 rpm. Both groups showed similar ($p < 0.05$) decreases in mean arterial (ET = -7.3%, HIIT = -4.5%), systolic (ET = -6.6%, HIIT = -8.8%), and diastolic (ET = -9.7, HIIT = -8.2%) blood pressure. HIIT decreased in LGSi (-33.7%) while ET did not change LGSi ($p > 0.05$). VO_{2max} increased ~25% with both HIIT and ET with no differences ($p > 0.05$)

between groups. These data suggest both HIIT and ET similarly decreased resting blood pressure and increased VO_{2max} while HIIT was effective in decreasing LGSI in subjects who were pre-hypertensive.

Table of Contents

List of Figures	vii
List of Tables	viii
Acknowledgements.....	ix
Chapter 1 - Introduction.....	1
Chapter 2 - Literature Review.....	2
Hypertension.....	2
Essential Hypertension.....	3
Prehypertension	4
Prehypertension and Disease	5
Blood Pressure and Aerobic Exercise Training.....	5
High Blood Pressure and Aerobic Exercise Training.....	6
Acute and Low-Grade Systemic Inflammation	7
Exercise Induced Inflammation	8
C-reactive Protein (CRP)	8
CRP as a Cardiac Risk Factor.....	9
CRP and Hypertension.....	10
CRP and Aerobic Exercise Training.....	11
High-intensity Interval Training.....	12
Chronic Training Adaptations.....	13
Interval Training for At-Risk Populations	13
Chapter 3 - Methods.....	16
Subjects.....	16
Experimental Design.....	16
Exercise Training.....	17
Experimental Measurements.....	18
Maximal Aerobic Capacity	18
Blood Sampling and Biochemical Analysis	19
Blood Pressure Measurements	19

Statistical Analysis	20
Chapter 4 - Results	21
Subjects	21
Training	21
Systemic Inflammation	28
Maximal Aerobic Capacity	30
Chapter 5 - Discussion	31
Mean Arterial Blood Pressure.....	31
Systemic Inflammation	34
Maximal Aerobic Capacity	35
Implications	36
Limitations	36
Future Directions	37
Conclusion	38
References	39

List of Figures

Figure 1: Mean Arterial Pressure	24
Figure 2: Systolic Blood Pressure	25
Figure 3: Diastolic Blood Pressure	26
Figure 4: Weekly Average Mean Arterial Blood Pressure	27
Figure 5: High-sensitivity C-reactive Protein	29

List of Tables

Table 1: Subject Characteristics.....	21
Table 2: Exercising Heart Rate	22
Table 3: Blood Pressure	23
Table 4: High-sensitivity C-reactive Protein	28
Table 5: VO _{2max} Data	30

Acknowledgements

This project was one of the greatest accomplishments in my life thus far. However, it must be noted that it wouldn't have been possible without the encouragement and support from many of my peers and family. Although I cannot truly express the thanks you deserve, I will surely try.

Mom, dad and Amy, thank you all for your encouragement. Not just with the project but throughout my life and the various avenues I have pursued. When all is said and done, the route I will have traveled will be far from a straight line, but your unconditional love and support has given me the confidence necessary to take the risks I have, and for that I will be forever grateful.

To my fellow graduate students, thanks for these past two years. The support both verbally and by actually helping in the lab whenever I needed it made what could have been a horribly stressful yearlong project much easier! The afternoon trips to the bowling alley to get some wind back in the sails, the late Thursday nights at Keltic Star and early Figure Friday mornings at Varsity Donuts, those are the things that I will remember from these past two years. I look forward to the days when I can tell my students how I had the privilege of working with the famous researcher they are reading about.

A specific thank you goes to the members of the Harms Lab. The weekly meetings were a huge help with this project. Whether it was helping form it in the early stages or acting as a test audience for the final presentation, you all were so willing to give your input in an effort to form a quality project. The familiar atmosphere offered a good environment where I knew I was going to be asked question, not to break me but to prepare me for when this was presented to the public, ultimately making the final presentation almost anti-climactic because I was so prepared.

Dr. Rosencranz and Josh, you two were there from the conception of the idea through the end so I thank you, specifically, for your help along the entire journey. Ariel, you were such a huge help as well. Your willingness to help with the training sessions made my life exponentially easier, so thank you.

And finally, Dr. Harms, thank you for everything. When I first approached you with idea of this training study you smiled. Initially, I was confused by that smile but I now know it was because you knew everything that went into it. But you let me pursue it and I am grateful you did. Along the way, you guided me into understand what science is truly about. Not publishing papers and getting grants, but cultivating answers for a question. You taught me to think holistically about issues and how to gain an appreciation for how health is not a product of one or two processes in the body but a complex relationship between many variables that can be influenced in so many ways. But most of all, you showed me why science is so exciting. Rarely, in other careers, do you get to develop your own idea and pursue it to an exhausting extent. But in science, that is what we do every day. We develop questions and ways to attempt to answer them. I had one questions when I started working under you a little over two years ago, but now the list has turned in to a small journal with no sign of shrinking. Thank you for inspiring me to continue to pursue these questions.

Chapter 1 - Introduction

Hypertension (HTN) has been linked to many major chronic diseases. Many diseases, if left uncontrolled, may lead to increased mortality. Prehypertension, an elevated blood pressure below the clinically diagnosable limit, has been shown to lead to HTN if left uncontrolled. However, through various lifestyle changes, factors contributing to elevated blood pressure can be well controlled. Exercise training has been shown to elicit beneficial adaptations which lead to increased metabolic health and cardiovascular function, including a decrease in elevated blood pressure. Traditionally, continuous aerobic exercise training (ET) has been the primary form of exercise therapy to achieve beneficial adaptations. However, in recent years, researchers have shown high intensity interval training (HIIT) to be a time efficient alternative to achieving similar physiological adaptations as ET. Additionally, recent research has shown that low-grade systemic inflammation (LGSI) can increase risk for cardiovascular disease including essential HTN. It has also been shown that exercise training, primarily high intensity exercise training, can decrease levels of LGSI. The majority of research with HIIT has used near-maximal work rates which may not be suitable for at-risk or diseased populations. Recently, a practical, low-volume interval training protocol has been developed to elicit similar metabolic adaptations as ET in subjects at-risk for the development of diabetes. However, this protocol has not been applied to other populations, such as hypertensive subjects. Therefore, the purpose of this study was to determine the effects of a low-volume, high intensity interval training protocol compared to ET on prehypertensive subjects. Additionally, this study investigated the effects of HIIT vs. ET on LGSI and how LGSI influenced MAP.

Chapter 2 - Literature Review

Hypertension

Normal blood pressure in healthy individuals is a systolic value of ≤ 120 mmHg and a diastolic value of ≤ 80 mmHg. Hypertension (HTN) is defined as blood pressure elevated from normal levels. Physiologically, this includes systolic and diastolic blood pressure higher than normal (22). However, HTN is clinically diagnosed when a patient's blood pressure has exceeded a systolic measurement of 139 mmHg and/or a diastolic measurement of 89 mmHg (22). HTN is typically classified as either essential or nonessential. Essential HTN is due directly to lifestyle choices and is proven to be a highly modifiable risk factor of heart disease, stroke, and all-cause mortality (132). Nonessential HTN is a result of a separate disease or disorder that has presented itself in the organism, such as renal disease or endocrinal disease. A third category of HTN is due to rare genetic disorders (22). This class has no significant contribution to the applicable portion of HTN in general population. For the purpose of this study, any reference to HTN is in regards to essential HTN unless otherwise noted.

Hypertension is commonly managed through pharmacological methods. Currently, 68% of those diagnosed with HTN are utilizing pharmaceutical therapy for treatment of HTN (90). The most widely prescribed type of drug for the control of HTN is an ACE inhibitor, which acts by inhibiting the angiotensin-converting enzyme which in turn prevents constriction of blood vessels (129). However, the benefits of ACE inhibition and ultimately preventing production of angiotensin II may be greater than decreasing blood pressure. In addition to preventing production of angiotensin II, ACE inhibitors may also decrease inflammation in the endothelial cells of the blood vessels (72). Angiotensin II has been shown to produce a superoxide anion in the smooth muscle and endothelial cells of the arterial vessels (54). Furthermore, angiotensin II

has been shown to increase the expression of certain pro-inflammatory cytokines (68). By increasing systemic cytokine activity there is potential for increasing the risk of HTN and cardiovascular disease as there has been strong association between LGSI and cardiovascular disease (CVD) risk (135).

Essential Hypertension

Essential HTN has an important economic impact on our nation. In 2008, the United States Department of Health and Human Services (USDHHS) reported that 29% of all Americans 18 years and older were hypertensive (90). In addition, the asymptomatic nature of HTN can cause many of those affected to go undiagnosed (90). Hypertension has severe implications aside from direct health outcomes. In 2010, the American Heart Association Statistics Committee released an update on heart disease and stroke statistics (75). Hypertension, and outcomes resulting from it, cost the United States \$76.6 billion dollars. This included medical care, pharmaceuticals, as well as days missed from work due to illness. With over 50% of American adults registering blood pressures above the threshold of healthy, this is a major issue in the state of our nation's health (75).

Although HTN is dictated greatly by lifestyle choices, there are also other non-modifiable factors that contribute to it. Factors such as age (47, 61, 62), race (15), gender (57), and familial history (82, 115) all have a role in the development of HTN. However, these factors are uncontrollable and unavoidable. In 2004, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure listed several lifestyle choices that could increase the risk of HTN including: excess body weight (obesity), excess dietary sodium intake, reduced physical activity, tobacco and alcohol use (22). In addition, this report indicates that primary prevention methods should aim to reduce or remove the lifestyle

factors associated with elevated blood pressure (22). Studies have suggested that a 2 mmHg reduction of diastolic blood pressure could cause a 17% decrease in the prevalence of HTN, a 14% reduction in mortality due to stroke and 9% reduction due to coronary heart disease leading to a 7% decrease in all-cause mortality nationally (26, 114, 132). Given that known lifestyle changes affect HTN, a greater emphasis on increasing physical activity and exercise is an attractive intervention.

Prehypertension

Prehypertension is clinically classified as having a systolic blood pressure in the range of 120-139 mmHg and/or a diastolic pressure between 80-89 mmHg (18). That is, a blood pressure elevated from what is considered normal or healthy, but not high enough to be clinically diagnosed as HTN. The term prehypertension was recently created in an effort to emphasize the clinical importance of this range of blood pressures (22). The rationale for this renaming was due in large part to the tendency for blood pressure to increase with age in industrialized society (120). The USDHHS reported an additional 28% of US adults being prehypertensive in addition to those diagnosed with HTN (90). Although there is often no clinical diagnosis for prehypertension, it remains a health issue. Researchers have shown in longitudinal data that men and women who were non-hypertensive at ages 55-65 had a 90% chance of becoming hypertensive if they lived to be 80-85 years old (126). More importantly, people who are 65 years or older have a 50% and 26% chance of becoming hypertensive in the next four years if they have blood pressures of 130-139/85-89mmHg and 120-129/80-85mmHg, respectively (127).

Prehypertension and Disease

Health is a continuum: optimal health on one end and severely unhealthy on the other end. With regards to blood pressure, if one does not clinically qualify as hypertensive, s/he may still in fact be unhealthy and at increased risk of disease. Lawes et al (2008) quantified the positive correlation that chronic disease has to above normal blood pressure (71). These authors found that high blood pressure, prehypertension and HTN, contributed to stroke (54% of subjects), ischemic heart disease (47%), hypertensive disease (75%) and other CVD (25%). Unfortunately, since prehypertension is not a diagnosable disease or disorder, subjects are still considered “healthy” while being at risk and have to wait for the onset of HTN or one of the other related diseases before treatment is prescribed. Qureshi et al (2005) similarly determined significant associations between prehypertension and cardiovascular disease (98). Of the over 5,000 prehypertensive subjects who participated in the Framingham Study, none had experienced myocardial infarction or stroke at the baseline measurement. Using 10 year follow up measurements, Qureshi and colleagues (2005) drew statistically significant associations between prehypertension and both myocardial infarction and coronary artery disease (98).

Blood Pressure and Aerobic Exercise Training

In 1992, The American Heart Association released a position statement describing the benefits of regular aerobic activity on hypertensive subjects (42). These benefits included controlling abnormalities in blood lipid levels and carbohydrate metabolism, increasing maximum ventilatory oxygen uptake and, specifically relating to cardiovascular health, beneficial changes in hemodynamic function such as increased vascular conductance (42). More recently, Whelton and colleagues (2002) published a meta-analysis of 53 randomized, controlled studies conducted between 1986 and 2000 to determine the effect of aerobic exercise on blood

pressure (133). In 45 supervised studies, a net decrease in both systolic and diastolic blood pressures, 4.23 and 2.68 mmHg respectively, was reported. Importantly, of the 53 studies analyzed, 27 studied participants who were not hypertensive, but likely prehypertensive (133).

High Blood Pressure and Aerobic Exercise Training

The beneficial effects of aerobic exercise on the control of blood pressure have been well researched (30, 38, 46, 64, 133). Researchers have shown that exercise at various intensities can alter many mechanisms responsible for reduced heart rate (3, 32, 33, 46, 137), increased stroke volume (25, 46, 89) and/or decreased total peripheral resistance (17, 46, 78, 113, 134). Aerobic exercise helps reduce resting heart rate, primarily through an altering of the parasympathetic and sympathetic outflows (3, 32, 33, 137). After exercise in healthy subjects there is an increase in vagal tone representing an increase in parasympathetic outflow (32). In unhealthy subjects, a decrease in sympathetic outflow occurs in addition to an increase in parasympathetic outflow, furthering the reduction in heart rate (3, 33). Along reduction in heart rate, stroke volume will increase due to an increase in production of plasma proteins and the Frank-Starling mechanism (25, 89). The primary effect of exercise on blood pressure is due to a reduction in total peripheral resistance (46). The mechanisms involved with a decrease in vascular resistance are likely norepinephrine and endothelial-1, both potent vasoconstrictors (17, 78, 113, 134). More recently, nitric oxide production and synthesis in the endothelial cells lining the vessels have shown to be significantly beneficial (65, 96). It is apparent, during various modes, intensities and durations of exercise, that aerobic exercise is beneficial to maintain or improve cardiovascular function, including HTN.

More recently, LGSII has been reported as a possible mechanism of atherosclerosis and vascular dysfunction (72, 79, 91, 135). In a sclerotic state, the vessel will have less compliance

leading towards a higher pressure as each pulse wave pushes through the vessel. Thus, it is important to consider LGSI as factor when discussing possible mechanisms involved in HTN.

Acute and Low-Grade Systemic Inflammation

Acute inflammation is a component of the non-specific immune response that occurs in response to injury or disease. In most cases inflammatory responses are self-limiting in which the body is able to regulate the levels of inflammation reached. However, some cases of inflammation cannot be controlled and result in chronic inflammatory diseases (39). Symptoms of acute inflammation are pain, heat, redness, swelling, and loss of function. Pain will only occur at the site of inflammation if the appropriate sensory nerves are present (20). The inflammatory response can involve many various plasma and cellular derived substances known as cytokines. The term cytokine refers to a large family of regulators produced throughout the body by many different cells (50). In the context of this paper, cytokine will refer to a modulator of the immune system. Often, an adverse reaction to an increase in cytokine activity is local inflammation. Sepsis is the classic model for researching this type of cytokine activity. In these models, after introduction of an inflammatory stimulus, the cytokines appear and can be detected systemically in the following order: tumor-necrosis factor alpha (TNF- α), Interleukin-1 beta (IL-1 β), Interleukin-6 (IL-6), Interleukin-1 receptor antagonist (IL-1ra), Interleukin-10 (IL-10), and soluble TNF- α receptors (sTNF-R) (2).

More recently, it is generally believed that a low-grade systemic inflammatory response is a primary process in the generation of conditions such atherosclerosis, obesity, type-2 diabetes and HTN (91). Low-grade systemic inflammation consists of elevated levels of the cytokines TNF- α , IL-1 β , IL-6, IL-1ra and sTNF-R (2, 31, 36, 72). Unlike sepsis, which elicits an exponential rise in cytokine activity of up to 100-fold, LGSI elicits a smaller two or three fold

response (95). The exact stimuli for cytokine production causing LGSI are unknown (27). It is hypothesized that atherosclerosis can be attributed to an accumulation of macrophages below the endothelial cells in blood vessels (36, 72). The accumulation of cells potentially causes an increase in external pressure as well as a decrease in local vascular health resulting in increased pressure and a less compliant vessel.

Exercise Induced Inflammation

As inflammation is the response to damaged tissue, certain inflammatory cytokines are also produced during exercise. However, unlike infections or LGSI, there is no initial increase in TNF- α or IL-1 during the inflammatory response. The first cytokine present during exercise is IL-6, which increases similar to values seen during the acute phase response (95). The release of IL-6 during exercise stimulates the release of IL-1ra, IL-10 (116), and sTNF-R, but not IL-1 β or TNF- α (123). In addition, IL-6 appears to be the primary factor inducing the release of hepatocyte-derived acute-phase proteins having anti-inflammatory properties (1). Despite the many cytokines involved in the pro- and anti-inflammatory responses, there is a single protein, C-reactive protein, which serves as a marker of inflammation not apparent until 8-12 hours following an inflammatory stimulus (95).

C-reactive Protein (CRP)

C-reactive protein (CRP) is an acute phase protein produced by hepatocytes and is circulating in all humans with levels that rise in response to inflammation. It was the first acute-phase protein to be discovered as a systemic marker of inflammation (92). In healthy humans, the mean level of CRP is 0.8 mg/L of blood, with the 90th centile at 3.0 mg/L. In an acute-phase stimulus, such as infection, levels can potentially increase up to 10,000 times baseline levels

(111), although an increase in CRP is not seen in the inflammatory response to exercise (95). During the acute-phase stimulus, CRP typically rises above normal limits within 6 hours, and peaks at 48 hours following event. The half-life of CRP is 19 hours in both healthy and inflamed states, thus the only determining factor of circulating CRP is the rate of synthesis which directly reflects the intensity of the stimulating process (128). Circulating CRP levels have no circadian rhythm (77) but may be influenced by certain diets (102). Reductions in CRP have been shown under low-carb (108), high plant sterols (60), alpha-linoleic acid rich (7), and Mediterranean style diets (37) while there has been a positive correlation made between CRP levels and glycemic load (74). Liver failure directly impairs CRP production due to impairment of hepatocytes. However, very few drugs affect CRP levels unless they also affect the pathological event initiating the acute-phase stimulus. Due to the resiliency of CRP, it serves as a very useful nonspecific marker of inflammation (92). In a clinical setting, the measurement being made is of high-sensitivity CRP (hs-CRP) (105). Many times these two types of proteins will be used interchangeably when discussing the relationship between systemic inflammation and risk of cardiovascular disease. The primary difference between CRP and hs-CRP is the measurement techniques used with hs-CRP are able to measure it in much lower levels allowing for greater detection of LGS (5).

CRP as a Cardiac Risk Factor

Recently in the scientific literature there has been debate if elevated CRP can be considered a risk factor or a risk marker of cardiovascular disease (135). The American Heart Association (AHA) and Center for Disease Controls (CDC) issued a statement regarding the use of CRP as a risk factor for CVD (91). In the statement is a set of criteria which the AHA and CDC use to describe desirable characteristics of a risk factor. Such criterion includes statistical

relevance as well as the ability to standardize testing and costs to the public. Of the various pro-inflammatory substances, the statement lists CRP as the best available test for assessing risk of CVD (91). In 1997, Ridker et al. conducted a longitudinal study hypothesizing that the risk of myocardial infarction and stroke, but not of venous thrombosis, was positively correlated to the baseline levels of CRP (104). The authors found that subjects with baseline values in the quartile with the highest levels of CRP had a higher relative risk for myocardial infarction and ischemic stroke than those in the lowest quartile. Thus, Ridker et al. (1997) concluded that there is a positive association with CRP and future cardiac events. Although systemic inflammation shows statistical associations with CVD risk, for clinical applications it would need to be validated against current measures. Ridker et al. (2000) conducted a longitudinal case-study of post-menopausal women assessing baseline levels of five different inflammatory markers as well as several lipid and lipoprotein measurements. These authors found, of all the markers measured, CRP was the strongest predictor of risk, greater than the more common measurement of ratio of total cholesterol to high-density lipoprotein (HDL), when compared as the lowest-quartile. In addition to current common measurements, based off the results of this study, measuring CRP levels in a clinical setting would better predict risk for cardiovascular events (101).

CRP and Hypertension

It has been well documented that HTN is a major risk factor associated with many of the leading causes of death due to disease (84). As mentioned, it has recently been shown that systemic inflammation may be related to atherosclerotic vessels (36). According to Poiseuille's Law, pressure is related to the radius of the cylinder that the fluid is moving through. With a hardened vessel wall, a less compliant vessel wall, the pressure will increase. In the cardiovascular system, this would result in an increase of blood pressure. Using data from one of

the most in-depth cardiovascular studies, the Framingham study, Ridker and colleagues (2000) made the observation that hs-CRP levels was the strongest predictor of future development of cardiovascular disease, including HTN, when compared to more common measurements such as total LDL cholesterol, total HDL cholesterol, and nine others (101). It has also been observed that the common pharmacological statin therapy has no effect on systemic inflammation in sclerotic vessels, although a reduction in LDL cholesterol can be seen (72) thus, leaving the vessel in a fibrotic state which still leads to HTN although in absence of hyperlipidemia. It has also been suggested that since total cholesterol and CRP act independently, hs-CRP assays may detect a different population at-risk leading to greater overall prediction of cardiovascular disease (135). In a clinical state, with the availability of hs-CRP assays, researchers have suggested adding it to the spectrum of blood tests done due to the cost-effectiveness in aiding the detection of possible disease (102, 103).

CRP and Aerobic Exercise Training

As aerobic exercise training has been shown to lower blood pressure, a common risk factor for CVD, decreases in markers of systemic inflammation can be seen post-exercise (80, 81, 119). Mattusch et al. (2000) studied moderately trained runners who were preparing for a marathon. The subjects trained 3-4 times per week, each session lasting 50 minutes at approximately 75% of the subject's lactate threshold. Mattusch found a decreased baseline CRP concentration in 10 of the 12 runners who completed training. This was contrary to the proposed hypothesis but strengthens the idea that exercise elicits an anti-inflammatory effect (80). Also, Stewart et al. (2007) conducted an exercise training study using treadmill running at 70-80% of heart rate reserve for 20 minutes in combination with a resistance training program that elicited momentary fatigue. Their subject pool consisted of both older and younger (71 ± 4 and 25 ± 5

years, respectively) who were classified as both active and inactive via self-report measures (119). The authors found a 58% decrease in serum CRP levels in the physically inactive subjects with no change in the active subjects, demonstrating that similar effects occur across different ages. Exercise-induced decreases in systemic inflammation can be seen in subjects who have already or currently have cardiovascular disease as well. Milani et al. recruited 235 subjects already suffering from coronary heart disease into a rehabilitation program that consisted of dietary controls and exercise training for three months (81). After three months, Milani et al. reported a similar decrease in CRP levels for subjects on and off of statin therapy, 42% and 38% respectively. The authors concluded that CRP, independent of other factors associated with exercise, will decrease significantly in subjects with coronary heart disease.

High-intensity Interval Training

Current American College of Sports Medicine (ACSM) guidelines state that the recommended amount of cardiorespiratory exercise training is at least 30 min/day on at least five days/week of moderate intensity or at least 20 minutes a day on three days/week of vigorous-intensity exercise for maintaining a healthy level of cardiorespiratory fitness (48). Previous studies have shown that brief, intense bouts of exercise elicit similar mitochondrial enzymatic responses (107), reduce glycogen utilization and lactate accumulation during matched-work exercise (12, 13), and can improve performance of activities heavily reliant on aerobic metabolism (34). Interval training, therefore, may be a time-efficient alternative to endurance training to present guidelines for healthy cardiorespiratory and metabolic adaptations (28).

Chronic Training Adaptations

High intensity interval training (HIIT) leads to many chronic adaptations. Chronic interval training protocols of various lengths, ranging from as short as six sessions over a two week span up to four sessions a week for 13 weeks, have increased maximal oxygen uptake (14, 23, 44, 55, 58, 59), decreased submaximal (44) and maximal exercising heart rate (23, 44), and increased time to fatigue (12-14). Though exercise protocols differed, similar mechanisms were triggered to cause the responses. Previous literature suggests the increase in oxygen uptake from training is intensity-dependent (52). Training bradycardia was possibly related to fewer afferent impulses arising (24) or an increase in stroke volume leading to a greater cardiac output per minute (58). The increased time to fatigue may be due to an increased efficiency (58) or in metabolic processes (12-14). Future research is still required to determine specific mechanisms responsible for these adaptations with HIIT. Although the optimal training protocol is still unknown, the benefits of HIIT training are apparent in the literature. However, it is less clear if similar benefits occur in at-risk or diseased populations or if this population is able to tolerate high intensity interval training.

Interval Training for At-Risk Populations

Although benefits of interval training have been reported in healthy populations (12-14, 44, 58), it is unclear if an at-risk population would be able to comply with vigorous bouts of exercise. Several studies using the similar volume of exercise (12-14, 73) used exercise protocols with very high intensities (~100% VO₂max) that would be far too difficult, and possibly dangerous for certain at-risk or diseased populations to perform. Specific with regards to HTN, ACSM has released a separate recommendation for cardiorespiratory maintenance calling for a lower intensity of exercise due to their potentially weakened cardiovascular system (94).

However, recent studies have shown potential for interval training to serve as a means to decreasing factors involved in the development or increasing the ability to manage HTN (23).

As mentioned earlier, a prehypertensive individual is considered at-risk for HTN and cardiac events due to the tendency for an increase of mean arterial pressure over time (120). Interval training has been shown to decrease risk factors in normotensive at-risk women (23), subjects who had already suffered a cardiovascular event (55, 136), and subjects undergoing cardiac rehabilitation (130). Exercise training elicited improvements in central and peripheral cardiovascular function (23, 55, 136), exercise tolerance (136), and increased aerobic capacity (55, 136). Additionally, subjects showed increases in submaximal values in VO₂, ventilation and exercising heart rate during the interval protocol (55) which potentially would all benefit individuals with HTN. According to the guidelines previously mentioned, these exercise protocols meet the recommended time commitment necessary to cause cardiovascular benefits. ACSM guidelines also state the primary barrier for noncompliance is the issue of time commitment (48). Assuming subjects who have or are nearing disease are not meeting the current guidelines, it is appropriate to explore even more time efficient means of reaching the physiological adaptations of the currently suggested exercise guidelines.

Hood et al. (2011) recently developed a low-volume interval training protocol tailored to sedentary, at-risk adults (59). Although not necessarily meeting the recommendations put forth by the ACSM, Hood and colleagues' protocol induced metabolic adaptations that reduced the risk of inactivity-related disorders in middle-aged adults who, prior to participation in the study, were considered sedentary (59). Although previous studies from their lab had shown similar results (73), their study remained novel because the subjects were middle-aged (45 ± 5 years)

sedentary subjects. The relative intensity was similar to a study by Guirard et al. (2011), suggesting that this is a safe protocol to exercise for at-risk as well as diseased populations.

In summary, prehypertension and HTN have many important health risks. It is known that aerobic exercise is a beneficial means of preventing and reversing the effects associated with HTN. Additionally, elevated levels of systemic inflammation are associated with increased prevalence of HTN and other cardiovascular risks. Previous literature also shows the benefits of aerobic exercise in relation to systemic inflammation. Recent evidence suggests possible cardiovascular benefits are associated with HIIT. In particular, an intriguing possibility exists for HIIT in managing HTN and determining how it compares with more conventional exercise approaches. Therefore, the purpose of this study was to determine the effects of high intensity interval training versus continuous aerobic exercise on subjects with prehypertension.

Additionally, we were interested in examining the influence of HIIT on LGSI and how this contributes to possible changes in blood pressure. We hypothesized that, due to the increased benefits seen with increased intensities, HIIT would show a greater decrease in mean arterial pressure than endurance training in pre-hypertensive subjects. In addition, due to greater reductions seen during high intensity exercise, we hypothesized HIIT would show a greater decrease in hs-CRP levels than endurance training in the same population.

Chapter 3 - Methods

Subjects

Fifteen pre-hypertensive subjects (3 men; 12 women) with elevated blood pressures (SBP: ≥ 120 mmHg, DBP: ≥ 80 mmHg) volunteered to participate. After being informed of the risks, subjects signed an informed consent waiver. No subjects had been previously diagnosed with clinical HTN and were apparently healthy as determined by standard pulmonary function tests and medical history questionnaire. All subjects were non-smokers, inactive (did not train at least one month prior to volunteering), and were free of heart and pulmonary disease determined via questionnaire. During the course of the study, three subjects dropped out due to schedule conflicts (n=2) and injuries not associated with this study (n=1). Therefore, a total of 12 subjects completed the protocol and were used in analysis. Subjects were encouraged to maintain their normal lifestyle, activity, and diets throughout the training period. All procedures were approved by the Institutional Review Board at Kansas State University, Manhattan, KS.

Experimental Design

The experimental protocol consisted of baseline testing, an 8-week training intervention, and post-training testing. Subjects visited the laboratory four times prior to training (BASE), 24-32 times for training sessions, and three times after the final session of training (POST). During the first visit, measurements of resting pulse rate and blood pressures, both systolic and diastolic, were performed. On the second visit, pulmonary function tests (PFT), an incremental maximum oxygen uptake test (VO_2 max) was performed in addition to blood samples taken for the measurement of systemic inflammation (high-sensitive C-reactive protein (hs-CRP)). Height,

weight, blood pressure, and pulse rates were measured the following visit. Following baseline testing, subjects were randomly assigned to either a high intensity interval training group (HIIT: n=7) or endurance training group (ET: n=5). Within four days, subjects performed a familiarization session of their designated training protocol and began an 8-week training period. Upon completion of training, subjects repeated visits two through four. After four weeks of training, subjects completed a VO_2max test in order to adjust the workload if necessary for any training effect.

Exercise Training

The training protocol was initiated at least two days following the familiarization bout. All subjects completed eight weeks of training. Both groups followed a standardized warm-up of three minutes pedaling at a cadence of 60rpm at 50% of the training workload. Specifically the training protocol used is one that has been previously used in an at risk population (59). Subjects following the ET protocol exercised four days a week, with at least two sessions per week being non-consecutive (i.e. training occurred on Monday, Tuesday, Thursday and Friday each week). Subjects completed 30 minutes of exercise at a workload equivalent to the 40% VO_2 reserve (VO_2R) on the cycle ergometer (Monark 818E) at a maintained cadence of 60 rpm. Subjects in the experimental group followed a HIIT protocol that has previously been used in at risk populations (73). Subjects performed a 1-to-1 work-to-rest ratio lasting 120 s on the cycle ergometer (Monark 828E). The bout was performed 10 times each session. The workload was set to 60% of peak power achieved during the $\text{VO}_{2\text{peak}}$ test. Following the termination of a session, subjects were allowed to cool-down at their own discretion, with workloads never being more than 50% of the training workload and never extending beyond five minutes. All training took

place in an exercise training lab within the Department of Kinesiology at Kansas State University and sessions were directly supervised.

Experimental Measurements

Maximal Aerobic Capacity

The incremental maximal oxygen uptake test was performed on a cycle ergometer (Sensormedics 800). Metabolic and ventilatory data were collected and analyzed continuously breath-by-breath throughout exercise (Sensormedics 229 Metabolic Cart, Sensormedics Corp., YorbaLinda, CA). A pulse oximeter (Datex-Ohmeda 3900P, Madison, WI) was used to estimate arterial oxygen saturation (SpO_2). Heart rate (HR) was continuously monitored via a chest strap heart rate monitor (Polar T31-Uncoded, Polar). Values from the modified Borg's rating of perceived exertion scale (RPE), measured 1-10, were recorded at each stage of exercise. After three minutes of rest, subjects began to warm up with unloaded cycling for one minute maintaining a cadence of 60-80 rpm. Following the warm up, the workload was increased by 25W every minute. Exercise was terminated when the subject was unable to maintain a cadence of 50 rpm for six seconds. All subjects were verbally encouraged to complete the test at the highest work rate possible. This value established the subject's peak oxygen consumption (VO_{2peak}).

Upon the termination of testing, subjects were removed from the ergometer for 15 minutes before attempting a second bout for validation of VO_{2max} . During the validation test, subjects began cycling at a cadence of 60-80 rpm while a workload equal to 110% of that reached previously was rapidly set. Subjects were encouraged to pedal until exhaustion, maintaining a cadence of 60-80 rpm.

Blood Sampling and Biochemical Analysis

Subjects sat quietly for five minutes before sample collection. Blood samples were collected via finger stick from the middle finger on their non-dominant hand. Prior to collection, the instrument was calibrated and subjects washed their hands with warm water and had their fingers massaged from the base to the tip several times. The finger stick site was then cleaned with alcohol and dried with a gauze pad. 50µm blood samples were collected in sterile lithium heparin coated capillary tubes within 10 seconds. hs-CRP was determined from whole blood samples which were applied to an hs-CRP cassette (Alere Cholestech LDX hs-CRP cassette, Alere San Diego, Inc., San Diego, CA). The cassette was then placed in the analyzer (Alere Cholestech LDX Analyzer, Alere San Diego, Inc., San Diego, CA) where the plasma was separated from the blood cells. Plasma was then incubated with a colloidal gold anti-CRP conjugate. The conjugate containing hs-CRP is captured by antibody while the remainder of the conjugate was discarded. A magnetic strip found on each cassette allowed the analyzer to calibrate and convert the reflectance reading (%R) to an hs-CRP concentration (mg/L).

Blood Pressure Measurements

Blood pressure measurement was taken at the brachial artery via manual plethysmography. Subjects were seated for at least 10 minutes at the time of measurement. Measurements were taken on three non-consecutive days each week for the entirety of the study. All measurements were made by the same researcher. A second researcher also made measurements during the pretesting, midpoint testing, and post testing phase to validate the original measures.

Statistical Analysis

SigmaStat 10 Statistical Software (Systat Software, Chicago, IL) was used for data analysis. Data is expressed as mean \pm SD. Statistical comparisons were corrected for unequal sample size by Bonferonni adjustment. Group differences were determined by a two-way mixed ANOVA with time as a repeated measurement. Relationships were determined via Pearson Product Moment Correlation. Significance was set at $p < 0.05$ for all analyses.

Chapter 4 - Results

Subjects

Subject characteristics are shown in Table 1. The men-to-women ratio was similar between groups (endurance training: m = 1, f = 4; high intensity interval training: m = 2, f = 7). There were no differences ($p>0.05$) in age, height, weight, or body mass index between groups

Table 1: Subject Characteristics

	ET (n=5)	HIIT (n=7)
Age (yrs)	33.8 ± 2.0	33.0 ± 7.4
Height (cm)	164.4 ± 6.2	170.6 ± 8.1
Weight (kg)	75.8 ± 13.0	86.0 ± 13.7
BMI (kg/m²)	28.3 ± 5.2	29.5 ± 3.8
MAP (mmHg)	98.4 ± 2.5	100.6 ± 5.4
Systolic Blood Pressure (mmHg)	124.2 ± 7.6	128.8 ± 8.2
Diastolic Blood Pressure (mmHg)	85.5 ± 1.5	86.5 ± 4.3
hs-CRP (mg/dL)	2.0 ± 1.7	3.2 ± 2.6
VO_{2max} (mL/kg/min)	22.9 ± 1.6	23.8 ± 3.5
HR_{rest} (bpm)	79.2 ± 10.0	81.1 ± 8.5

Values are presented as mean ± SD
hs-CRP = high-sensitivity C-reactive protein
MAP = mean arterial pressure

Training

Training adherence was 100% for all subjects across all training sessions. The total time per training week for HIIT (39 minutes) was 29.6% of time spent training by ET (132 minutes). Average training heart rate for both groups is shown in Table 2. By design, HR values were significantly higher for HIIT compared to ET throughout training. The workload averaged 80.5 ± 23.3W (range 50-135W) for ET and 119.6 ± 24.3W (range 90-165W) for HIIT. Average intensity during training was ~68% VO_{2max} during ET and ~93% VO_{2max} during HIIT. The average amount of work per week was over two times greater ($p<0.05$) in ET (579.6 ± 41.9kJ)

than in HIIT (215.3 ± 14.6 kJ). Height, weight and body mass index did not change ($p > 0.05$) with training.

Table 2: Exercising Heart Rate

	Day 1	Day 2	Day 3	Day 4	Average
Endurance					
Week 1	140.2 ± 15.7	143.9 ± 15.5	141.2 ± 20.2	139.0 ± 19.8	141.1 ± 2.1
Week 2	139.0 ± 17.9	141.0 ± 17.0	137.0 ± 17.6	132.2 ± 15.0	137.3 ± 3.8
Week 3	134.8 ± 13.7	139.4 ± 13.4	131.5 ± 15.5	134.1 ± 16.8	134.9 ± 3.3
Week 4	131.8 ± 12.4	135.8 ± 16.4	130.4 ± 15.3	128.9 ± 20.0	131.8 ± 2.9
Week 5		147.3 ± 17.6	150.1 ± 20.2	143.7 ± 18.0	147.1 ± 3.2
Week 6	136.4 ± 19.1	137.6 ± 15.3	137.6 ± 20.4	136.3 ± 16.3	137.0 ± 0.7
Week 7	131.8 ± 15.8	137.4 ± 16.6	138.5 ± 22.2	136.2 ± 16.8	136.0 ± 3.0
Week 8	142.6 ± 16.8	137.7 ± 16.9	141.5 ± 19.8	142.9 ± 17.5	141.2 ± 2.4
HIIT					
Week 1	165.6 ± 19.4	169.7 ± 20.5	161.4 ± 18.5		$165.6 \pm 4.2^*$
Week 2	157.5 ± 17.1	156.8 ± 17.4	155.6 ± 17.8		$156.6 \pm 0.9^*$
Week 3	156.6 ± 16.9	145.8 ± 20.0	150.8 ± 25.8		$151.1 \pm 5.4^{*\wedge}$
Week 4	156.4 ± 17.5	150.8 ± 23.0	151.7 ± 18.0		$153.0 \pm 1.7^{*\wedge}$
Week 5		160.5 ± 15.9	157.2 ± 16.3		158.9 ± 1.4
Week 6	153.0 ± 15.5	153.5 ± 13.9	159.9 ± 17.3		$155.5 \pm 2.2^*$
Week 7	157.4 ± 17.6	155.2 ± 14.2	155.1 ± 13.6		$155.9 \pm 0.8^*$
Week 8	153.8 ± 17.0	156.0 ± 16.1	153.3 ± 19.2		$154.4 \pm 0.8^*$

Values are presented as mean \pm SD

*significantly different from ET; $p < 0.05$

\wedge significantly different from Week 1; $p < 0.05$

Note: Week 5, Day 1 is blank due to subjects performing a VO₂max test that session. HIIT was limited to three days a week so there are no Day 4 values.

Arterial Blood Pressure

Table 3 shows ET and HIIT resting blood pressures and resting heart rates for pre-, after 4 weeks and after 8 weeks. Figure 1 shows the individual and mean responses of resting mean arterial pressure prior to, after 4 weeks and after 8 weeks of training. Figure 2 shows individual and mean responses of systolic blood pressure (SBP) prior to, after 4 weeks and after 8 weeks of

training. Figure 3 shows individual and mean responses of diastolic blood pressure (DBP) prior to, after 4 weeks and after 8 weeks of training. Groups were well matched with no significant differences in their baseline values. Both training groups showed similar ($p < 0.05$) reductions in MAP from baseline of -4.5 to -7.3% (5 of 5 subjects in ET and 6 of 7 subjects in HIIT) at 4 weeks and 8 weeks. After 4 weeks of training, reductions in SBP of ~5% from baseline occurred in 5 of 5 subjects in ET and 6 of 7 subjects in HIIT. There was a further decrease ($p < 0.05$) in HIIT after the week 8, but not ($p > 0.05$) in ET. DBP decreased ($p < 0.05$) during the fourth week of training in ET but not ($p > 0.05$) with HIIT. After week 8, DBP decreased significantly from baseline in HIIT with no further ($p > 0.05$) decrease from week 4 in ET. The weekly averages of MAP (Figure 4A), SBP (Figure 4B), and DBP (Figure 4C) are shown for both ET and HIIT. At week 7, DBP was significantly higher in HIIT compared to ET. No difference occurred at any other time ($p > 0.05$).

Table 3: Blood Pressure

	ET (n=5)			HIIT (n=7)		
	Pre	4 Weeks	8 Weeks	Pre	4 Weeks	8 Weeks
MAP (mmHg)	98.4 ± 2.5	91.2 ± 5.5*	87.7 ± 7.7*	101.0 ± 6.2	96.5 ± 5.8*	92.4 ± 5.6*
SBP (mmHg)	124.2 ± 7.6	116.0 ± 6.2*	112.4 ± 8.8*	129.0 ± 9.2	123.1 ± 6.8*	117.7 ± 7.0 [^]
DBP (mmHg)	85.5 ± 1.5	77.2 ± 5.8*	73.6 ± 7.4*	86.8 ± 5.3	83.1 ± 5.6	79.7 ± 6.2*
HR_{Rest} (bpm)	79.2 ± 10.0	66.6 ± 8.8*	65.8 ± 6.7*	81.1 ± 9.2	75.9 ± 9.2	71.6 ± 9.5*
PP (mmHg)	38.8 ± 8.1	38.0 ± 3.7	38.4 ± 1.7	42.2 ± 5.1	38.7 ± 4.2	38.0 ± 6.7

Values are presented as mean ± SD

*significantly different from Pre; $p < 0.05$

[^]significantly different from 4 weeks; $p < 0.05$

MAP = mean arterial pressure, SBP = systolic blood pressure, DBP = diastolic blood pressure,

HR_{Rest} = resting heart rate, PP = pulse pressure

Figure 1: Mean Arterial Pressure

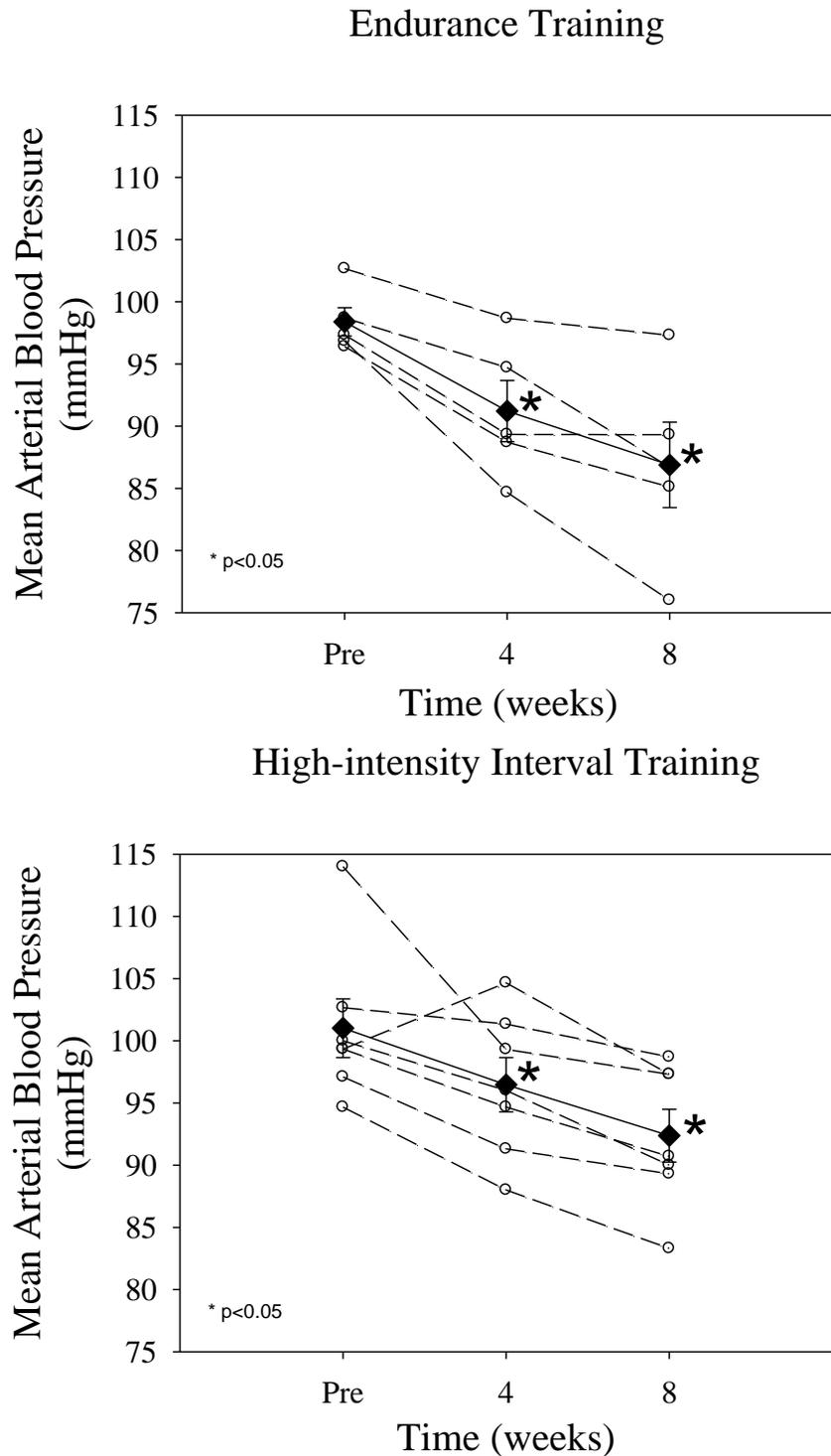


Fig. 1: Individual (open circles) and mean (filled diamonds) MAP responses to training. Both ET and HIIT showed similar decreases at 4 wks. from baseline (approximately -7.3% and -4.5% respectively, $p < 0.05$) with no further decrease at 8 wks.

* significantly different from Pre; $p < 0.05$

Figure 2: Systolic Blood Pressure

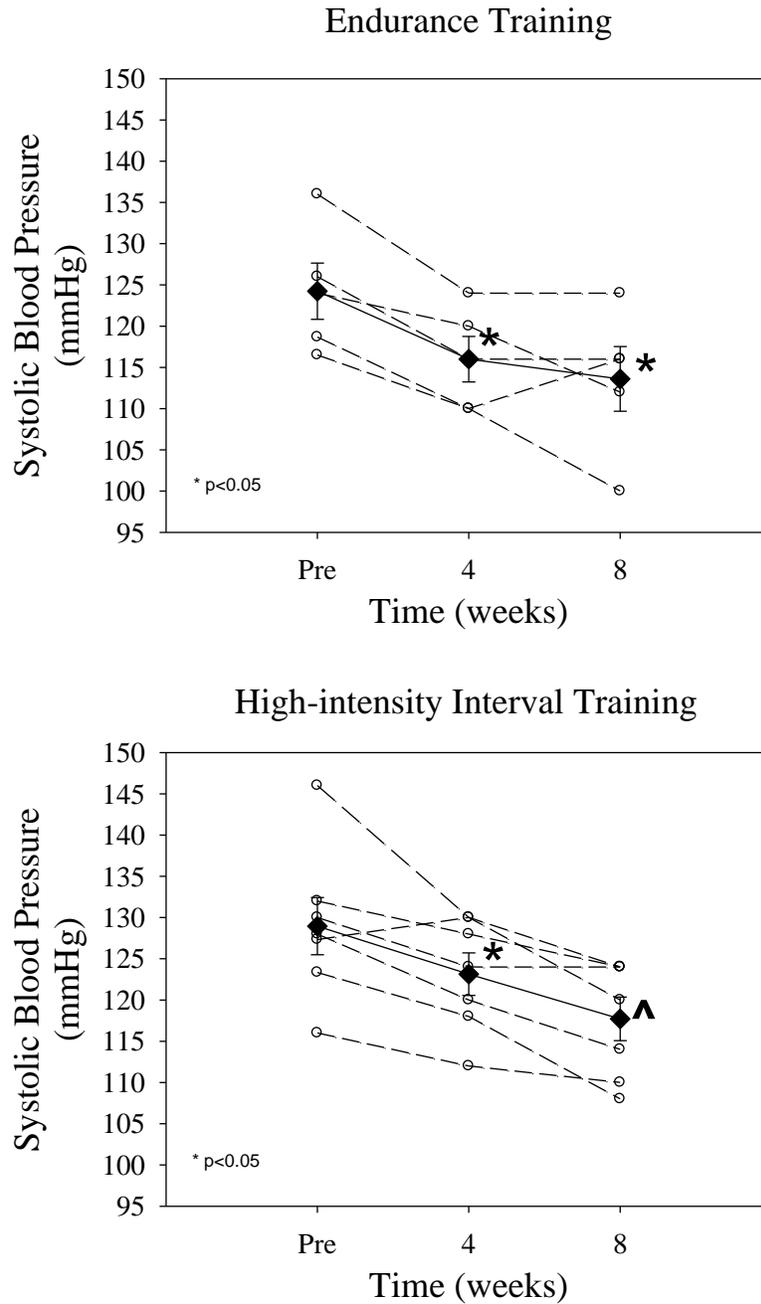


Fig. 2: Individual (open circles) and mean (filled diamonds) systolic blood pressure responses to training. Both ET and HIIT showed similar decreases at 4 wks. from baseline (approximately - 6.6% and -4.6% respectively, $p<0.05$). HIIT showed a further decrease at 8 wks. from 4 wks. (approximately -4.4%, $p<0.05$) while ET show no further decrease.

* significantly different from Pre; $p<0.05$

+ significantly different from 4 weeks; $p<0.05$

^ significantly different from ET; $p<0.05$

Figure 3: Diastolic Blood Pressure

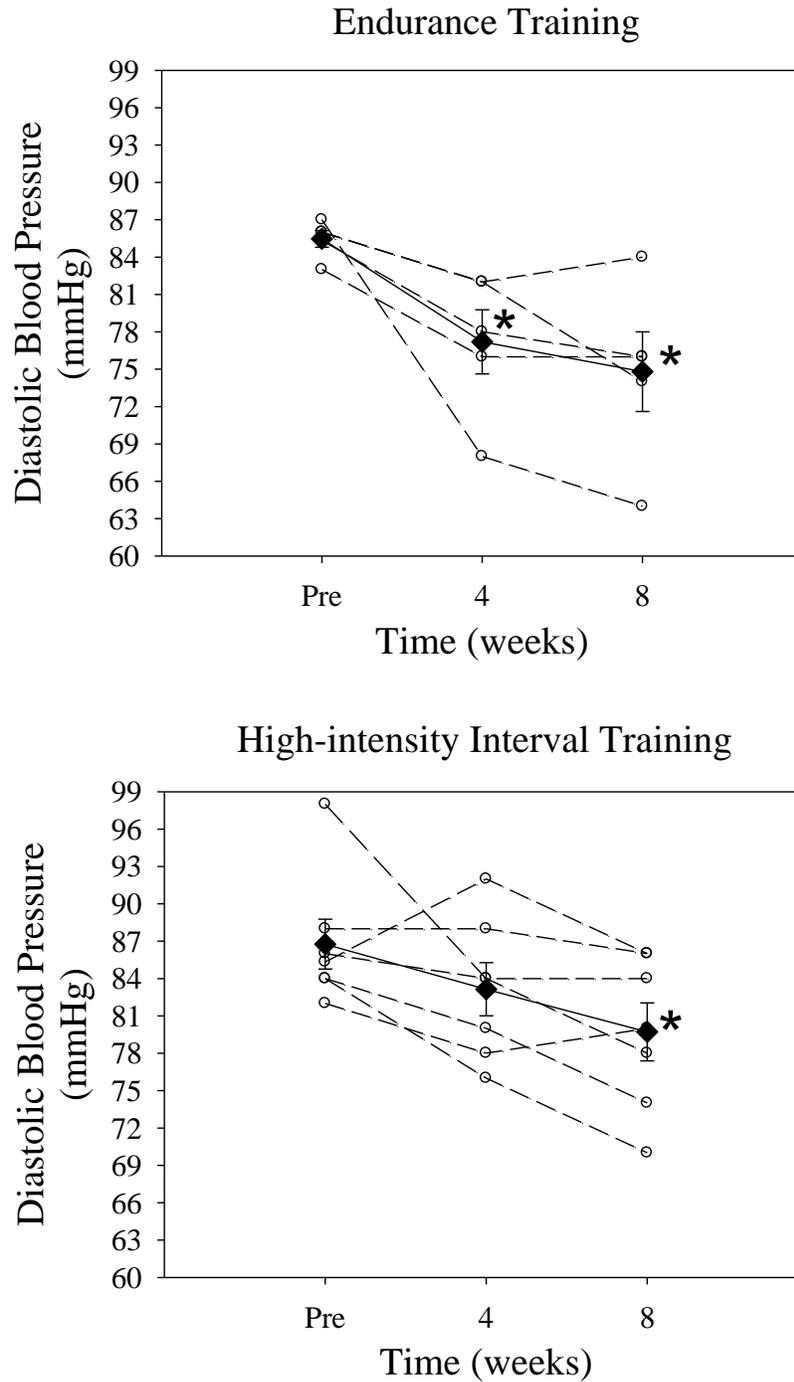


Fig. 3: Individual (open circles) and mean (filled diamonds) diastolic blood pressure responses to training. ET showed a decrease at 4 wks. from baseline (approximately -9.7%, $p < 0.05$) with no further decrease at 8 wks. HIIT showed a decrease at 8 wks. from baseline (approximately -8.2%, $p < 0.05$).

* significantly different from Pre; $p < 0.05$

Figure 4: Weekly Average Mean Arterial Blood Pressure

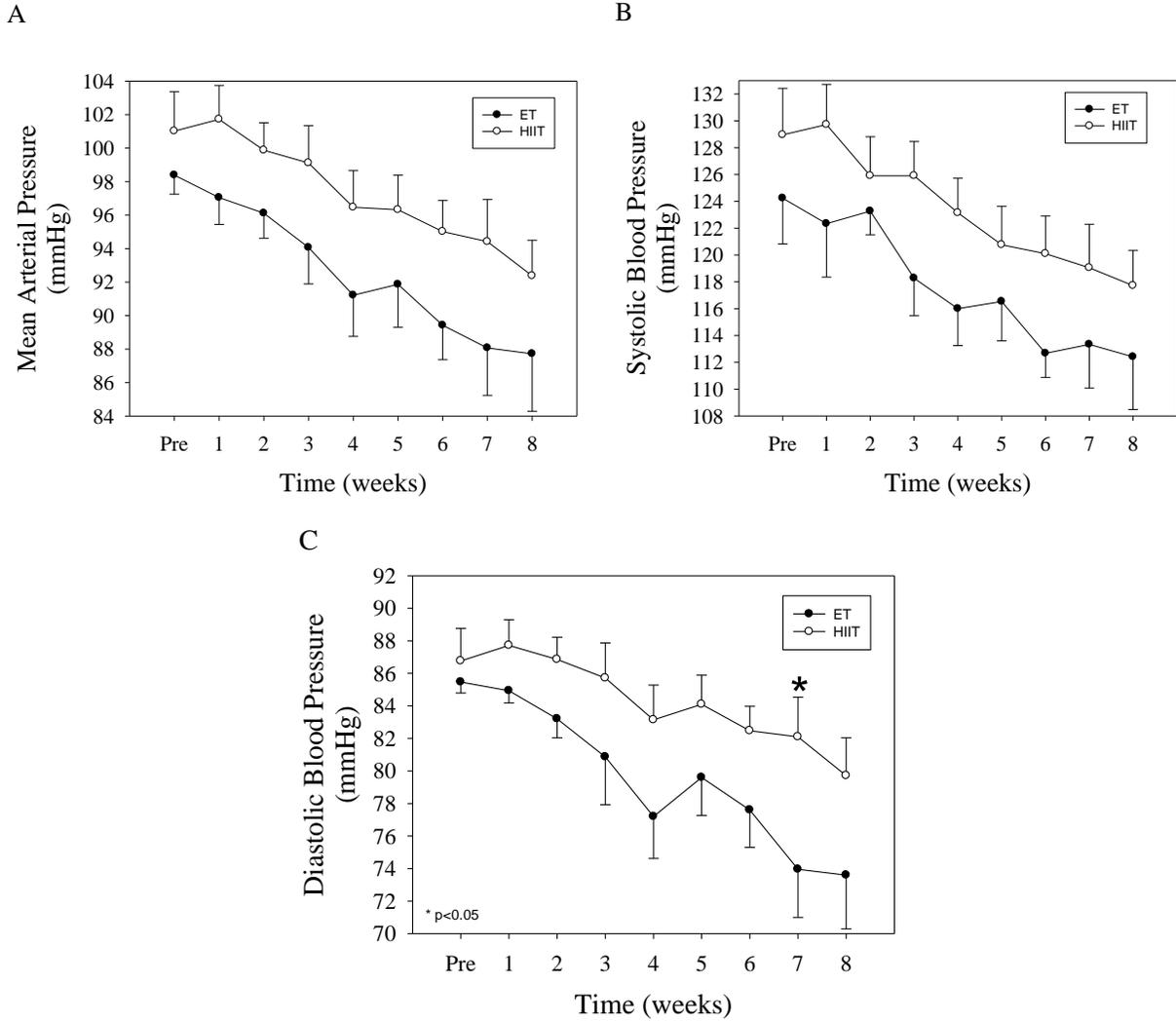


Fig. 4: Group mean time course for mean arterial pressure (A), systolic blood pressure (B), and diastolic blood pressure (C). Fig. 4A: There were no group differences ($p > 0.05$) during training. Fig. 4B: There were no group differences ($p > 0.05$) during training. Fig. 4C: ET had a significantly greater decrease from Week 6 to 7 than HIIT (approximately -4.6% and 0% respectively, $p < 0.05$). All other times were not different ($p > 0.05$) between groups. * significantly different from ET; $p < 0.05$

Systemic Inflammation

Table 4 shows mean ET and HIIT high-sensitivity C-reactive protein, as a marker of systemic inflammation levels, for pre-, 4 weeks and after 8 weeks. Figure 5 shows individual (open circles) and mean (closed circles) CRP responses over the course of training. There was no difference ($p>0.05$) between groups prior to training. There was a decrease ($p<0.05$) in hs-CRP after 4 weeks and after 8 weeks from baseline in HIIT with no changes ($p>0.05$) in ET after 4 weeks or after 8 weeks. There was no relationship ($r=0.04$) between the decrease in hs-CRP ($p>0.05$) and change in MAP. Additionally, there was no relationship ($r=0.09$) between baseline levels of hs-CRP ($p>0.05$) and MAP in the subjects. This is not in agreement of previous literature using crossover data from an epidemiological approach.

Table 4: High-sensitivity C-reactive Protein

	ET (n=5)	HIIT (n=7)
Pre	1.97 ± 1.66	3.23 ± 2.80
4 week	1.80 ± 1.53	1.81 ± 1.82*^
8 week	1.26 ± 1.01	2.14 ± 2.01*^

Values are presented as mean ± SD

*significantly different from Pre; $p<0.05$

^significantly different from ET; $p<0.05$

Figure 5: High-sensitivity C-reactive Protein

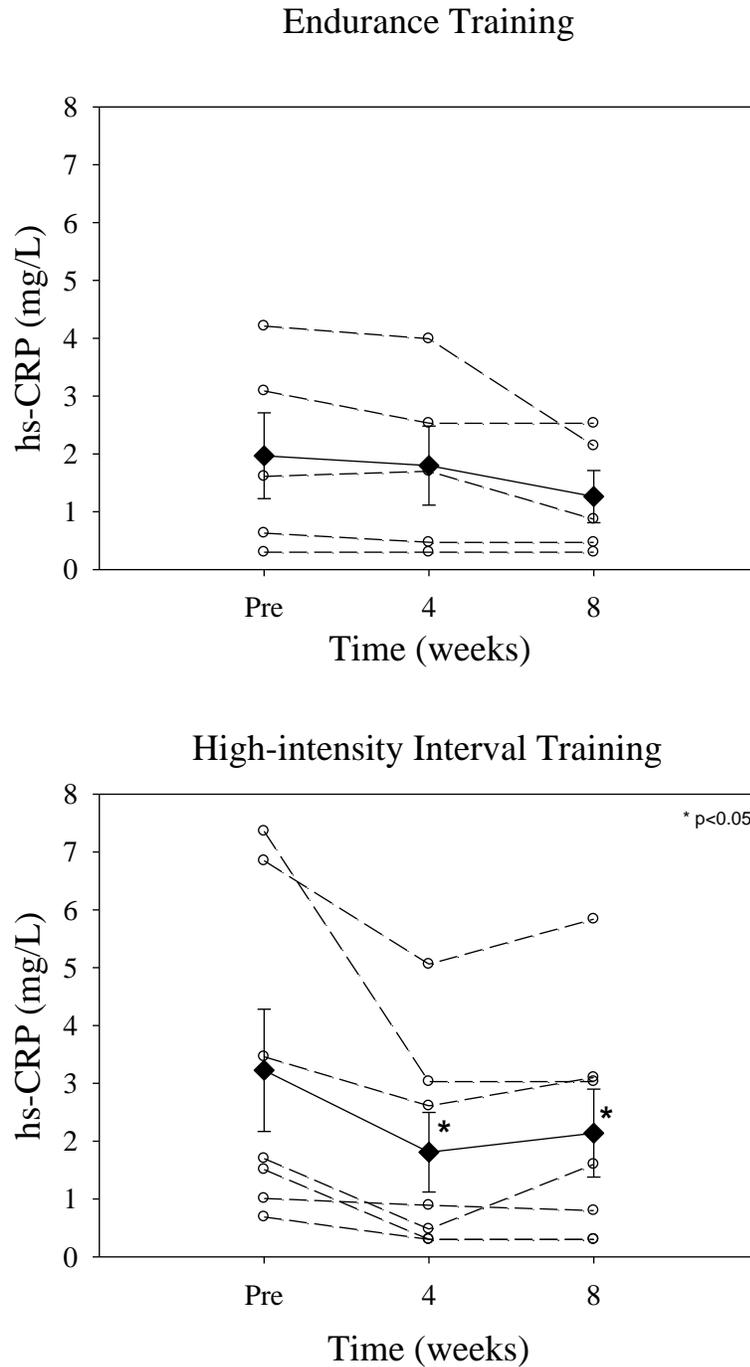


Fig. 5: Individual (open circles) and mean (filled diamonds) hs-CRP responses to training. A decrease from baseline ($p<0.05$) is seen at 4wk in HIIT with no further decrease at 8wk. No decrease from baseline ($p>0.05$) is seen in ET.

* significantly different from Pre; $p<0.05$

Maximal Aerobic Capacity

Table 5 shows ET and HIIT data during the VO_{2max} test. VO_2 , VCO_2 , VE, HR and workload increased ($p < 0.05$) from pre-training values after 4 weeks of training in ET with no further increases ($p > 0.05$) following 8 weeks of training. VCO_2 , VE and workload increased ($p < 0.05$) in HIIT after 4 weeks of training. Following 8 weeks of training, VO_2 (mL/kg/min) significantly increased ($p < 0.05$) as well. The increase in VO_2 with training was ~25% for both groups. There were no between group differences ($p > 0.05$) in any variables at any point during the study.

Table 5: VO_{2max} Data

Time	ET (n=5)			HIIT (n=7)		
	Pre	4 Weeks	Post	Pre	4 Weeks	Post
VO_2 (L/min)	1.69 ± 0.17	2.02 ± 0.18*	2.17 ± 0.22*	2.05 ± 0.23	2.31 ± 0.22	2.32 ± 0.24
VO_2 (mL/kg/min)	22.2 ± 1.1	27.3 ± 1.9*	29.6 ± 2.8*	23.7 ± 1.5	27.0 ± 1.9	27.3 ± 1.8*
VCO_2 (L/min)	2.02 ± 0.20	2.50 ± 0.20*	2.58 ± 0.23*	2.40 ± 0.29	2.74 ± 0.28*	2.72 ± 0.27*
VE (L/min)	77.2 ± 9.2	90.3 ± 7.1*	96.8 ± 11.2*	88.8 ± 10.4	107.2 ± 11.4*	109.9 ± 12.5*
RER	1.17 ± 0.03	1.27 ± 0.03	1.20 ± 0.03	1.17 ± 0.04	1.19 ± 0.02	1.19 ± 0.03
VE/ VCO_2	38.2 ± 1.8	36.3 ± 1.66	37.4 ± 2.40	37.4 ± 2.07	39.2 ± 1.8	40.2 ± 1.4
VE/ VO_2	45.9 ± 3.7	45.1 ± 3.24	44.8 ± 3.77	43.7 ± 3.11	46.5 ± 2.5	47.4 ± 1.9
HR _{peak} (bpm)	162.8 ± 2.3	174.6 ± 6.0*	175.6 ± 6.0*	175.6 ± 5.4	180.9 ± 3.9	179.4 ± 4.3
Peak Workload (Watts)	170 ± 17	200 ± 14*	205 ± 12*	182 ± 16	207 ± 15*	211 ± 14*

Values are presented as mean ± SD

*significantly different from Pre; $p < 0.05$

VO_2 = aerobic capacity, VCO_2 = CO_2 production, VE = ventilation, RER = respiratory exchange ratio, VE/ VCO_2 = ventilatory efficiency, VE/ VO_2 = ventilatory equivalent

Chapter 5 - Discussion

The purpose of this study was to compare the effects of high intensity interval training (HIIT) vs. endurance training (ET) on mean arterial blood pressure (MAP) and a marker of LGSI in pre-hypertensive subjects. Our data suggest that, contrary to our hypothesis, both exercise protocols were equally effective in decreasing MAP, systolic blood pressure (SBP), and diastolic blood pressure (DBP); however systemic inflammation was improved only with HIIT. Also HIIT was equally as effective as ET in improving aerobic capacity. Importantly, these effects seen with HIIT occurred with substantially less total exercise time and volume than ET. HIIT, therefore, may be a time efficient alternative form of training compared to the more traditional endurance training approach in reducing blood pressure in pre-hypertensive subjects which has additional health benefits of reducing systemic inflammation.

Mean Arterial Blood Pressure

Eight weeks of chronic exercise training, either HIIT or ET, led to a reduction in mean arterial blood pressure of approximately 9%, which is in agreement with previous studies that used endurance trained subjects over a similar period of time as in our study (22, 120). Additionally, systolic (SBP), diastolic (DBP) blood pressures, and resting heart rate decreased with both HIIT and ET. While specific mechanisms for these improvements in blood pressure with exercise training were not measured in our study, previous literature allows for some insight to possibilities. The decrease in SBP and DBP can potentially be due to a combination of central cardiac and peripheral adaptations. MAP is a product of cardiac output and systemic vascular resistance. With regard to cardiac output, both training protocols in our study led to a resting

bradycardia which was anticipated. Exercise induced bradycardia has been attributed to a combination of an increased vagal tone (9) as well as a potential increase in plasma volume leading to increase in stroke volume via the Frank-Starling mechanism (25, 51). Since our study lasted only 8 weeks, it is unlikely that ventricular reconstruction, typically associated with traditional exercise training, occurred (93). However, changes seen in the periphery, according to Poiseuille's Law (131), are likely due to a change in the radius of the vessel. Beneficial adaptations leading to a decreased systemic vascular resistance are likely due to three reasons (46): vascular responsiveness (21, 66, 70, 78), neural (11, 43, 67), or structural adaptations (16, 109, 110, 125). Therefore, the reduction in resting MAP we observed is consistent with previous reports. However, we believe our data are the first to demonstrate that HIIT was equally effective as ET in the decrease of MAP in pre-hypertensive subjects.

Why was HIIT as effective as ET in reducing blood pressure? First, the reduction in resting heart rate due to chronic exercise was expected (112). Previous literature has shown that the magnitude of the decrease in HR may be dependent on the intensity of the exercise performed (76, 85). However, in previous studies, the total volume of work performed was not tightly controlled, so a conclusive stance could not be made (10, 122). One study, from Pichot et al. (2005), reported that decreased resting HR was attributed to increased parasympathetic nerve activity (PSNA) (97). The exercise that was performed by their subjects totaled 180 minutes over 4 days was greater in duration than our protocol. Thus it is likely that a significant contributor to reduced MAP with HIIT was training induced brachycardia.

A second reason for reduced blood pressure with HIIT is improved stroke volume. HIIT allows subjects to challenge the pumping ability of the heart more than at continuous, lower intensities. While one previous study found no differences in SV adaptations with interval

training (45), more recent research disagrees (35, 56, 87). For example, a reported decrease in left-ventricular (LV) end-systolic volume and increase in LV ejection fraction occurred after 12 weeks of exercise training (136). Although the subjects were heart failure patients, in comparison to the control group performing ET, the benefits were greater with HIIT. The exact mechanism causing the increase is not presently known however, HIIT therefore, likely led to increased stroke volume in our subjects.

The third possibility for decreased MAP with HIIT is decreased systemic vascular resistance (SVR), an indicator of peripheral vascular function. In diseased subjects, SVR is greater than healthy subjects due to endothelial dysfunction (100). There are several potential mechanisms involved in the generation of this dysfunction, including an increase in inflammatory cytokines and/or decrease in nitric oxide (NO). This area of HIIT adaptations is largely unexplored, but NO has been shown to have a significant response (53). The exact modulators of NO production and synthesis are currently being investigated (41), but with regard to HIIT, we believe shear stress effects on NO production to be a plausible mechanism.

Shear stress increases endothelial nitric oxide synthase (eNOS) expression and activity (29, 99). The increase in eNOS has been shown to cause an increase in NO-dependent vasodilation in hypercholesterimics, a common diagnostic measure of HTN (19). Shear stress is caused by fluid passing across endothelial cells. It has been shown to be dependent on intensity in that higher intensity exercise causes a faster flow, thus causing a greater shear rate (124, 136). The increase in shear rate, resulting in an increase in NO-dependent vasodilation would result in a sustained decrease in vascular resistance. Of the factors contributing to MAP, a decrease in SVR via increased shear stress would potentially have the greatest effect. We believe that this is

a likely key mechanism responsible for the decrease in MAP with HIIT. This theory obviously requires future testing to determine whether or not it occurs with HIIT.

During HIIT, subjects pedaled at rates of ~100rpm, which also may have contributed to reduce BP. The effect of pedal frequency during upright exercise on exercising blood pressure and the baroreflex has recently been investigated. Ogoh (2007) demonstrated a resetting of the baroreflex dependent on pedal frequency during upright exercise (88). They reported a downward and leftward shift of the baroreceptor curve, allowing for lower blood pressure during exercise pedaling at 80 rpm when compared to 60 rpm. The authors propose that feedback from the cardiopulmonary baroreceptor can modulate the arterial baroreceptor activity. An increase in pedal frequency would cause an increase in central volume (106). The altering of the baroreceptor activity would lead to a decrease in exercising blood pressure.

Systemic Inflammation

An unexpected finding was that there was no relationship observed between baseline CRP levels, as a marker of systemic inflammation, and baseline MAP in either training group. Additionally, it was unexpected that there was no relationship between the decrease in CRP and decrease in MAP following training for either HIIT or ET. This was surprising given epidemiological evidence that reported a relationship between these variables (36, 101, 102), although one study found no relationship (6). However, in previous literature, increased systemic inflammation was related to HTN, not necessarily prehypertension. Since our subjects were prehypertensive and not diagnosed with HTN, the amount of systemic inflammation was likely less than those with HTN and thus there would be less opportunity for improvement with training. But, if that is the case, why did we see a decrease in inflammation in HIIT? The mechanism may be IL-6. According to Nielsen et al. (1996), IL-6 is present in higher concentrations after

repeated bouts of maximal exercise (86). It has also been shown that increases in IL-6 are present later and in lower concentrations after submaximal exercise due to a smaller amount of muscle mass recruited (63, 117, 118). As referenced earlier, IL-6 derived from exercising muscle is independent of TNF- α but still triggers other anti-inflammatory cytokines (95). Therefore, due to an increased amount of muscle mass recruited with HIIT, greater IL-6 may have been secreted from the exercising muscle which led to increases in anti-inflammatory cytokines.

Maximal Aerobic Capacity

The similar improvements in maximal aerobic capacity (VO_{2max}) with HIIT compared to ET in our study are consistent with previous reports and a commonly reported finding (23, 28, 34, 58). It has been shown that increases in VO_{2max} following training are typically intensity dependent (121). Recently, many studies also show that improvements in VO_{2max} can occur with minimal training volume at near maximal-intensities (12-14). In addition to similar changes in VO_{2max} , HIIT has been shown to increase mean power output, time to fatigue, and decrease time to completion in time trials highlighting the potential performance benefits associated with interval training (12-14, 49). To further the significance of the findings, it should be noted that the absolute work done during HIIT by our subjects was markedly less (~90%) than ET, 225-315 kJ/week versus 2250-3250 kJ/week respectively. However, exercise in the severe domain can be uncomfortable for subjects which can act as a barrier for compliance. The protocol used in our study was designed to be attainable by many populations, either healthy or of compromised health (73). The intensity was low enough to be achievable by un-trained individuals, but over the 1 min intervals, high enough to achieve near maximal heart rate. As it is well known that aerobic capacity is a direct indicator of one's health (40), the relative ease of this protocol makes it highly attractive in disease populations and populations who are not prone to exercise.

Implications

The primary implication of this study is the ability for subjects with prehypertension to decrease their elevated blood pressure and systemic inflammation that may cause dysfunction in the arterial vasculature. The results of our study also have the potential to overcome the time barrier that historically limits exercise in subjects at risk for developing HTN (48). HIIT elicited improvements in aerobic capacity and cardiovascular health. Previous studies also confirm improvements in aerobic capacity, and metabolic improvements (59, 73). Therefore, this training protocol has the potential to be prescribed in a clinical setting to prevent the development of chronic diseases such as HTN or diabetes. Since we also reported a decrease in systemic inflammation with HIIT, the potential also exists for this exercise protocol to serve as a therapeutic measure for inflammatory diseases such as arthritis. Furthermore, this training protocol furthers the possibility for HIIT to be a staple in cardiac rehabilitation. Although limited research has been conducted thus far (136), the low volume and relatively lower intensity may be enticing to this diseased population.

Limitations

Several limitations exist which may have affected our results. First, we did not monitor the subjects' activity levels and diet outside of the training session. Increased leisure time physical activity (69) and dietary intake of sodium (8) have been shown to affect cardiovascular health. While our subjects were strongly encouraged to not change their daily activities during testing, we do not know if this was the case. Secondly, hs-CRP measurements were made only once during pre, 4 wks, and 8 wks due to financial reasons. Since hs-CRP can vary due to multiple reasons, such as acute illness with no reported symptoms, at least two tests would provide a more reliable value (102). However, we ensured that testing conditions were tightly

controlled so the changes we observed likely were due to exercise training. Also, reduction in body fat following training may have contributed to reduced systemic inflammation. While body weight didn't change with training in our subjects, we don't know if changes in lean body mass or fat mass occurred. Finally, human error may have affected the measurement of blood pressure, which was manually taken. However, in an attempt to ensure accurate assessment, blood pressure measurements were periodically validated by an independent investigator. Furthermore, the change in MAP with training that we observed is consistent with previous literature (81).

Future Directions

To our knowledge this is the first study to investigate the effects of HIIT on MAP in subjects with prehypertension. The exercise protocol we followed has been used in prior studies to examine the effects on muscle metabolism (59, 73). With positive outcomes in both previous and the present study, we would suggest further investigation on the stimulus responsible for these outcomes. We have speculated on possible mechanisms involved, but direct measurement is necessary to gain a better understanding. It would be novel to explore resting baroreceptor activity after chronic training at high pedal frequency with HIIT. In regards to changes in systemic inflammation, it would be worthwhile to investigate other markers of inflammation, specifically IL-6. It is important to understand any differences seen using the same time pattern at different intensities, or if slightly modifying the work-to-rest ratio would change the results. It is also important to test different subject populations under this protocol. The current study used pre-hypertensive, but not hypertensive, population. In order for this protocol to be prescribed clinically, experiments will need to be performed using populations with HTN. More importantly, if this protocol is to be used as a time-efficient alternative to the ACSM recommendations, it is necessary to gain an understanding of the effects seen during a longer

prescribed time. To our knowledge, this is the longest application of this specific training protocol. However, it is necessary to look at the effects seen using this protocol for 6 months, a year, etc. Also, as childhood obesity has become a recent concern (4), the comorbidity of obesity is also a concern (i.e. diabetes, HTN) (83). It would be a novel approach to apply this exercise protocol to overweight/obese children in an attempt to reverse some negative health outcomes seen as this protocol has shown positive metabolic and, in our study, cardiovascular adaptations.

Conclusion

Chronic exercise training is known to help to reduce HTN. Interval training has been shown in recent years to be a healthy, time-efficient alternative to traditional endurance exercise training in regulation of glucose and insulin levels as well as improve gas exchange at the level of the tissue. Results from our study suggest that high intensity interval training can also be as effective as more traditional endurance training in reducing blood pressure in subjects with prehypertension. An additional benefit with HIIT above ET is that HIIT may be more effective than ET in reducing systemic inflammation, which may be contributing to HTN. Further research is needed to determine the specific mechanistic basis for these improvements and their implications to populations already effected by HTN.

References

1. **Akira S.** IL-6 and NF-IL6 in Acute-Phase Response and Viral Infection. *Immunol.Rev.* 127: 1: 25-50, 1992.
2. **Akira S, Taga T and Kishimoto T.** Interleukin-6 in biology and medicine. *Adv.Immunol.* 54: 1-78, 1993.
3. **Amano M, Kanda T, Ue H and Moritani T.** Exercise training and autonomic nervous system activity in obese individuals. *Med.Sci.Sports Exerc.* 33: 8: 1287-1291, 2001.
4. **Anderson PM and Butcher KF.** Childhood obesity: trends and potential causes. 16: 1: 19-45, 2006.
5. **Bassuk SS, Rifai N and Ridker PM.** High-sensitivity C-reactive protein: clinical importance. *Curr.Probl.Cardiol.* 29: 8: 439-493, 2004.
6. **Bautista L, Vera L, Arenas I and Gamarra G.** Independent association between inflammatory markers (C-reactive protein, interleukin-6, and TNF- α) and essential hypertension. *J.Hum.Hypertens.* 19: 2: 149-154, 2004.
7. **Bemelmans W, Lefrandt J, Feskens E, van Haelst P, Broer J, Meyboom-de Jong B, May J, Tervaert JC and Smit A.** Increased α -linolenic acid intake lowers C-reactive protein, but has no effect on markers of atherosclerosis. *Eur.J.Clin.Nutr.* 58: 7: 1083-1089, 2004.
8. **Bibbins-Domingo K, Chertow GM, Coxson PG, Moran A, Lightwood JM, Pletcher MJ and Goldman L.** Projected effect of dietary salt reductions on future cardiovascular disease. *N.Engl.J.Med.* 362: 7: 590-599, 2010.
9. **Blomqvist CG and Saltin B.** Cardiovascular adaptations to physical training. *Annu.Rev.Physiol.* 45: 1: 169-189, 1983.

10. **Braith RW, Pollock ML, Lowenthal DT, Graves JE and Limacher MC.** Moderate-and high-intensity exercise lowers blood pressure in normotensive subjects 60 to 79 years of age. *Am.J.Cardiol.* 73: 15: 1124-1128, 1994.
11. **Brown MD, Dengel DR, Hogikyan RV and Supiano MA.** Sympathetic activity and the heterogenous blood pressure response to exercise training in hypertensives. *J.Appl.Physiol.* 92: 4: 1434-1442, 2002.
12. **Burgomaster KA, Heigenhauser GJF and Gibala MJ.** Effect of short-term sprint interval training on human skeletal muscle carbohydrate metabolism during exercise and time-trial performance. *J.Appl.Physiol.* 100: 6: 2041-2047, 2006.
13. **Burgomaster KA, Hughes SC, Heigenhauser GJF, Bradwell SN and Gibala MJ.** Six sessions of sprint interval training increases muscle oxidative potential and cycle endurance capacity in humans. *J.Appl.Physiol.* 98: 6: 1985-1990, 2005.
14. **Burgomaster KA, Howarth KR, Phillips SM, Rakobowchuk M, MacDonald MJ, McGee SL and Gibala MJ.** Similar metabolic adaptations during exercise after low volume sprint interval and traditional endurance training in humans. *J.Physiol.(Lond.)* 586: 1: 151-160, 2008.
15. **Burt VL, Whelton P, Roccella EJ, Brown C, Cutler JA, Higgins M, Horan MJ and Labarthe D.** Prevalence of hypertension in the US adult population results from the Third National Health and Nutrition Examination Survey, 1988-1991. *Hypertension* 25: 3: 305-313, 1995.
16. **Cameron JD and Dart AM.** Exercise training increases total systemic arterial compliance in humans. 266: 2: H693-H701, 1994.

17. **Cardillo C, Kilcoyne CM, Waclawiw M, Cannon RO and Panza JA.** Role of endothelin in the increased vascular tone of patients with essential hypertension. *Hypertension* 33: 2: 753-758, 1999.
18. **Carretero OA and Oparil S.** Essential hypertension: Part I: definition and etiology. *Circulation* 101: 3: 329-335, 2000.
19. **Casino PR, Kilcoyne CM, Quyyumi AA, Hoeg JM and Panza JA.** The role of nitric oxide in endothelium-dependent vasodilation of hypercholesterolemic patients. *Circulation* 88: 6: 2541-2547, 1993.
20. **Chandrasoma P and Taylor CR.** Part A. General Pathology, Section II. The Host Response to Injury, Chapter 3. The Acute Inflammatory Response, sub-section Cardinal Clinical Signs. 2005.
21. **Chen H and Chiang I.** Chronic exercise decreases adrenergic agonist-induced vasoconstriction in spontaneously hypertensive rats. 271: 3: H977-H983, 1996.
22. **Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL, Jones DW, Materson BJ, Oparil S and Wright Jr JT.** Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension* 42: 6: 1206-1252, 2003.
23. **Ciolac EG, Bocchi EA, Bortolotto LA, Carvalho VO, Greve JM and Guimarães GV.** Effects of high-intensity aerobic interval training vs. moderate exercise on hemodynamic, metabolic and neuro-humoral abnormalities of young normotensive women at high familial risk for hypertension. 33: 8: 836-843, 2010.
24. **Clausen J, Trap-Jensen J and Lassen N.** The effects of training on the heart rate during arm and leg exercise. 26: 3: 295-301, 1970.

25. **Convertino V, Brock P, Keil L, Bernauer E and Greenleaf J.** Exercise training-induced hypervolemia: role of plasma albumin, renin, and vasopressin. *J.Appl.Physiol.* 48: 4: 665-669, 1980.
26. **Cook NR.** Implications of small reductions in diastolic blood pressure for primary prevention. *Arch.Intern.Med.* 155: 7: 701, 1995.
27. **Coppack SW.** Pro-inflammatory cytokines and adipose tissue. 60: 349-356, 2001.
28. **Coyle EF.** Very intense exercise-training is extremely potent and time efficient: a reminder. *J.Appl.Physiol.* 98: 6: 1983-1984, 2005.
29. **Davis ME, Cai H, Drummond GR and Harrison DG.** Shear stress regulates endothelial nitric oxide synthase expression through c-Src by divergent signaling pathways. *Circ.Res.* 89: 11: 1073-1080, 2001.
30. **Dickinson HO, Mason JM, Nicolson DJ, Campbell F, Beyer FR, Cook JV, Williams B and Ford GA.** Lifestyle interventions to reduce raised blood pressure: a systematic review of randomized controlled trials. *J.Hypertens.* 24: 2: 215-233, 2006.
31. **Dinarello CA.** Interleukin-1 and interleukin-1 antagonism. *Blood* 77: 8: 1627-1652, 1991.
32. **Dixon EM, Kamath MV, McCartney N and Fallen EL.** Neural regulation of heart rate variability in endurance athletes and sedentary controls. *Cardiovasc.Res.* 26: 7: 713-719, 1992.
33. **Duncan JJ, Farr JE, Upton SJ, Hagan RD, Oglesby M and Blair SN.** The effects of aerobic exercise on plasma catecholamines and blood pressure in patients with mild essential hypertension. 254: 18: 2609-2613, 1985.
34. **Eddy DO, Sparks KL and Adelizi DA.** The effects of continuous and interval training in women and men. *Eur.J.Appl.Physiol.Occup.Physiol.* 37: 2: 83-92, 1977.

35. **Ehsani A, Biello DR, Schultz J, Sobel BE and Holloszy J.** Improvement of left ventricular contractile function by exercise training in patients with coronary artery disease. *Circulation* 74: 2: 350-358, 1986.
36. **Epstein FH and Ross R.** Atherosclerosis—an inflammatory disease. *N.Engl.J.Med.* 340: 2: 115-126, 1999.
37. **Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, D'Armiento M, D'Andrea F and Giugliano D.** Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome. 292: 12: 1440-1446, 2004.
38. **Fagard RH and Cornelissen VA.** Effect of exercise on blood pressure control in hypertensive patients. 14: 1: 12-17, 2007.
39. **Ferrero-Miliani L, Nielsen O, Andersen P and Girardin S.** Chronic inflammation: importance of NOD2 and NALP3 in interleukin-1 β generation. 147: 2: 227-235, 2007.
40. **Fleg JL, Morrell CH, Bos AG, Brant LJ, Talbot LA, Wright JG and Lakatta EG.** Accelerated longitudinal decline of aerobic capacity in healthy older adults. *Circulation* 112: 5: 674-682, 2005.
41. **Fleming I and Busse R.** Molecular mechanisms involved in the regulation of the endothelial nitric oxide synthase. 284: 1: R1-R12, 2003.
42. **Fletcher GF, Blair SN, Blumenthal J, Caspersen C, Chaitman B, Epstein S, Falls H, Froelicher ES, Froelicher VF and Pina IL.** Statement on exercise. Benefits and recommendations for physical activity programs for all Americans. A statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart association. *Circulation* 86: 1: 340-344, 1992.

43. **Floras JS and Hara K.** Sympathoneural and haemodynamic characteristics of young subjects with mild essential hypertension. *J.Hypertens.* 11: 6: 647, 1993.
44. **Fox EL, Bartels RL, Billings CE, O'Brien R, Bason R and Mathews D.** Frequency and duration of interval training programs and changes in aerobic power. *J.Appl.Physiol.* 38: 3: 481-484, 1975.
45. **Fox EL, Bartels RL, Billings CE, O'Brien R, Bason R and Mathews D.** Frequency and duration of interval training programs and changes in aerobic power. *J.Appl.Physiol.* 38: 3: 481-484, 1975.
46. **Franklin BA and Fagard R.** Position stand. 195: 9131/04: 3603-0533, 2004.
47. **Franklin SS, Gustin IV W, Wong ND, Larson MG, Weber MA, Kannel WB and Levy D.** Hemodynamic patterns of age-related changes in blood pressure: the Framingham Heart Study. *Circulation* 96: 1: 308-315, 1997.
48. **Garber C, Blissmer B, Deschenes M, Franklin B, Lamonte M, Lee I, Nieman D and Swain D.** American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med.Sci.Sports Exerc.* 43: 7: 1334, 2011.
49. **Gibala MJ, Little JP, Van Essen M, Wilkin GP, Burgomaster KA, Safdar A, Raha S and Tarnopolsky MA.** Short-term sprint interval versus traditional endurance training: similar initial adaptations in human skeletal muscle and exercise performance. *J.Physiol.(Lond.)* 575: 3: 901-911, 2006.
50. **Gilman AG, Goodman K and Gilman A.** *The pharmacological Basis of therapeutics.* Macmillan Publishing Co., 1980.

51. **Goodman JM, Liu PP and Green HJ.** Left ventricular adaptations following short-term endurance training. *J.Appl.Physiol.* 98: 2: 454-460, 2005.
52. **Gormley SE, Swain DP, High R, Spina RJ, Dowling EA, Kotipalli US and Gandrakota R.** Effect of Intensity of Aerobic Training on $\dot{V}O_2 \text{ max}$. *Med.Sci.Sports Exerc.* 40: 7: 1336, 2008.
53. **Green DJ, Maiorana A, O'Driscoll G and Taylor R.** Effect of exercise training on endothelium-derived nitric oxide function in humans. *J.Physiol.(Lond.)* 561: 1: 1-25, 2004.
54. **Griendling KK, Ushio-Fukai M, Lassègue B and Alexander RW.** Angiotensin II signaling in vascular smooth muscle new concepts. *Hypertension* 29: 1: 366-370, 1997.
55. **Guiraud T, Nigam A, Juneau M, Meyer P, Gayda M and Bosquet L.** Acute responses to high-intensity intermittent exercise in CHD patients. *Med.Sci.Sports Exerc.* 43: 2: 211-217, 2011.
56. **Hagberg JM, Ehsani A and Holloszy J.** Effect of 12 months of intense exercise training on stroke volume in patients with coronary artery disease. *Circulation* 67: 6: 1194-1199, 1983.
57. **He J and Whelton PK.** Epidemiology and prevention of hypertension. *Med.Clin.North Am.* 81: 5: 1077-1097, 1997.
58. **Helgerud J, Hoydal K, Wang E, Karlsen T, Berg P, Bjerkaas M, Simonsen T, Helgesen C, Hjorth N and Bach R.** Aerobic High-Intensity Intervals Improve $\dot{V}O_2 \text{ max}$ More Than Moderate Training. *Med.Sci.Sports Exerc.* 39: 4: 665, 2007.
59. **Hood MS, Little JP, Tarnopolsky MA, Myslik F and Gibala MJ.** Low-volume interval training improves muscle oxidative capacity in sedentary adults. *Med.Sci.Sports Exerc.* 43: 10: 1849-1856, 2011.

60. **Jenkins DJ, Kendall CW, Marchie A, Faulkner DA, Wong JM, de Souza R, Emam A, Parker TL, Vidgen E and Lapsley KG.** Effects of a dietary portfolio of cholesterol-lowering foods vs lovastatin on serum lipids and C-reactive protein. *290: 4: 502-510, 2003.*
61. **Kannel WB and Gordan T.** Evaluation of cardiovascular risk in the elderly: the Framingham study. *Bull.N.Y.Acad.Med.* 54: 6: 573, 1978.
62. **Kannel WB and Gordon T.** *The Framingham study: an epidemiological investigation of cardiovascular disease.* US Department of Health, Education, and Welfare, National Institutes of Health, 1968.
63. **Keller C, Steensberg A, Pilegaard H, Osada T, Saltin B, Pedersen BK and Neufer PD.** Transcriptional activation of the IL-6 gene in human contracting skeletal muscle: influence of muscle glycogen content. *15: 14: 2748-2750, 2001.*
64. **Kelley GA, Kelley KA and Vu Tran Z.** Aerobic exercise and resting blood pressure: a meta-analytic review of randomized, controlled trials. *4: 2: 73-80, 2001.*
65. **KINGWELL BA.** Nitric oxide-mediated metabolic regulation during exercise: effects of training in health and cardiovascular disease. *14: 12: 1685-1696, 2000.*
66. **KINGWELL BA.** Nitric oxide-mediated metabolic regulation during exercise: effects of training in health and cardiovascular disease. *14: 12: 1685-1696, 2000.*
67. **Kohno K, Matsuoka H, Takenaka K, Miyake Y, Okuda S, Nomura G and Imaizumi T.** Depressor effect by exercise training is associated with amelioration of hyperinsulinemia and sympathetic overactivity. *Intern.Med.* 39: 12: 1013, 2000.
68. **Kranzhöfer R, Schmidt J, Pfeiffer CA, Hagl S, Libby P and Kübler W.** Angiotensin induces inflammatory activation of human vascular smooth muscle cells. *Arterioscler.Thromb.Vasc.Biol.* 19: 7: 1623-1629, 1999.

69. **Lakka TA, Venalainen JM, Rauramaa R, Salonen R, Tuomilehto J and Salonen JT.** Relation of leisure-time physical activity and cardiorespiratory fitness to the risk of acute myocardial infarction in men. *N.Engl.J.Med.* 330: 22: 1549-1554, 1994.
70. **Laughlin MH, Schrage WG, McAllister RM, Garverick H and Jones A.** Interaction of gender and exercise training: vasomotor reactivity of porcine skeletal muscle arteries. *J.Appl.Physiol.* 90: 1: 216-227, 2001.
71. **Lawes C, Hoorn SV and Rodgers A.** Global burden of blood-pressure-related disease, 2001. *371: 9623: 1513-1518*, 2008.
72. **Libby P, Ridker PM and Maseri A.** Inflammation and atherosclerosis. *Circulation* 105: 9: 1135-1143, 2002.
73. **Little JP, Safdar A, Wilkin GP, Tarnopolsky MA and Gibala MJ.** A practical model of low-volume high-intensity interval training induces mitochondrial biogenesis in human skeletal muscle: potential mechanisms. *J.Physiol.(Lond.)* 588: 6: 1011-1022, 2010.
74. **Liu S, Manson JE, Buring JE, Stampfer MJ, Willett WC and Ridker PM.** Relation between a diet with a high glycemic load and plasma concentrations of high-sensitivity C-reactive protein in middle-aged women. *Am.J.Clin.Nutr.* 75: 3: 492-498, 2002.
75. **Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K and Gillespie C.** Heart disease and stroke statistics—2010 update. *Circulation* 121: 7: e46-e215, 2010.
76. **Loimaala A, Huikuri H, Oja P, Pasanen M and Vuori I.** Controlled 5-mo aerobic training improves heart rate but not heart rate variability or baroreflex sensitivity. *J.Appl.Physiol.* 89: 5: 1825-1829, 2000.

77. **Macy EM, Hayes TE and Tracy RP.** Variability in the measurement of C-reactive protein in healthy subjects: implications for reference intervals and epidemiological applications. *Clin.Chem.* 43: 1: 52-58, 1997.
78. **Maeda S, Miyauchi T, Kakiyama T, Sugawara J, Iemitsu M, Irukayama-Tomobe Y, Murakami H, Kumagai Y, Kuno S and Matsuda M.** Effects of exercise training of 8 weeks and detraining on plasma levels of endothelium-derived factors, endothelin-1 and nitric oxide, in healthy young humans. *Life Sci.* 69: 9: 1005, 2001.
79. **Mahmud A and Feely J.** Arterial stiffness is related to systemic inflammation in essential hypertension. *Hypertension* 46: 5: 1118-1122, 2005.
80. **Mattusch F, Dufaux B, Heine O, Mertens I and Rost R.** Reduction of the plasma concentration of C-reactive protein following nine months of endurance training. *Int.J.Sports Med.* 21: 01: 21-24, 2000.
81. **Milani RV, Lavie CJ and Mehra MR.** Reduction in C-reactive protein through cardiac rehabilitation and exercise training. *J.Am.Coll.Cardiol.* 43: 6: 1056-1061, 2004.
82. **Munger RG, Prineas RJ and Gomez-Marin O.** Persistent elevation of blood pressure among children with a family history of hypertension: the Minneapolis Children's Blood Pressure Study. *J.Hypertens.* 6: 8: 647, 1988.
83. **Must A, Spadano J, Coakley EH, Field AE, Colditz G and Dietz WH.** The disease burden associated with overweight and obesity. 282: 16: 1523-1529, 1999.
84. **National Center for Health Statistics.** Health, United States, 2010: With Special Feature on Death and Dying. 2011.

85. **Nemoto K, Gen-no H, Masuki S, Okazaki K and Nose H.** Effects of high-intensity interval walking training on physical fitness and blood pressure in middle-aged and older people. 82: 803-811, 2007.
86. **Nielsen HB, Secher NH, Christensen NJ and Pedersen BK.** Lymphocytes and NK cell activity during repeated bouts of maximal exercise. 271: 1: R222-R227, 1996.
87. **Oberman A, Fletcher GF, Lee J, Nanda N, Fletcher BJ, Jensen B and Caldwell ES.** Efficacy of high-intensity exercise training on left ventricular ejection fraction in men with coronary artery disease (the Training Level Comparison Study). *Am.J.Cardiol.* 76: 10: 643-647, 1995.
88. **Ogoh S, Fisher JP, Fadel PJ and Raven PB.** Increases in central blood volume modulate carotid baroreflex resetting during dynamic exercise in humans. *J.Physiol.(Lond.)* 581: 1: 405-418, 2007.
89. **Oscai LB, Williams BT and Hertig BA.** Effect of exercise on blood volume. *J.Appl.Physiol.* 24: 5: 622-624, 1968.
90. **Ostchega Y, Yoon SS, Hughes J and Louis T.** Hypertension awareness, treatment, and control--continued disparities in adults: United States, 2005-2006. *NCHS Data Brief* (3): 3: 1-8, 2008.
91. **Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon III RO, Criqui M, Fadd YY, Fortmann SP, Hong Y and Myers GL.** Markers of inflammation and cardiovascular disease. *Circulation* 107: 3: 499-511, 2003.
92. **Pepys M and Baltz ML.** Acute phase proteins with special reference to C-reactive protein and related proteins (pentaxins) and serum amyloid A protein. *Adv.Immunol.* 34: 141, 1983.

93. **Peronnet F, Ferguson R, Perrault H, Ricci G and Lajoie D.** Echocardiography and the athlete's heart. *9: 5: 102-112, 1981.*
94. **Pescatello LS.** Exercise and hypertension: recent advances in exercise prescription. *Curr.Hypertens.Rep. 7: 4: 281-286, 2005.*
95. **Petersen AMW and Pedersen BK.** The anti-inflammatory effect of exercise. *J.Appl.Physiol. 98: 4: 1154-1162, 2005.*
96. **Pialoux V, Brown AD, Leigh R, Friedenreich CM and Poulin MJ.** Effect of cardiorespiratory fitness on vascular regulation and oxidative stress in postmenopausal women. *Hypertension 54: 5: 1014-1020, 2009.*
97. **Pichot V, Roche F, Denis C, Garet M, Duverney D, Costes F and Barthélémy J.** Interval training in elderly men increases both heart rate variability and baroreflex activity. *15: 2: 107-115, 2005.*
98. **Qureshi AI, Suri MFK, Kirmani JF, Divani AA and Mohammad Y.** Is prehypertension a risk factor for cardiovascular diseases? *Stroke 36: 9: 1859-1863, 2005.*
99. **Ranjan V, Xiao Z and Diamond SL.** Constitutive NOS expression in cultured endothelial cells is elevated by fluid shear stress. *269: 2: H550-H555, 1995.*
100. **Ribeiro F, Alves AJ, Duarte JA and Oliveira J.** Is exercise training an effective therapy targeting endothelial dysfunction and vascular wall inflammation? *Int.J.Cardiol. 141: 3: 214-221, 2010.*
101. **Ridker PM, Hennekens CH, Buring JE and Rifai N.** C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N.Engl.J.Med. 342: 12: 836-843, 2000.*

102. **Ridker PM.** C-reactive protein a simple test to help predict risk of heart attack and stroke. *Circulation* 108: 12: e81-e85, 2003.
103. **Ridker PM and Cook N.** Clinical usefulness of very high and very low levels of C-reactive protein across the full range of Framingham Risk Scores. *Circulation* 109: 16: 1955-1959, 2004.
104. **Ridker PM, Cushman M, Stampfer MJ, Tracy RP and Hennekens CH.** Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N.Engl.J.Med.* 336: 14: 973-979, 1997.
105. **Rifai N, Ballantyne CM, Cushman M, Levy D and Myers GL.** Point: High-Sensitivity C-Reactive Protein and Cardiac C-Reactive Protein Assays: Is There a Need to Differentiate? *Clin.Chem.* 52: 7: 1254-1256, 2006.
106. **Rowell LB.** *Human cardiovascular control.* Oxford University Press, USA, 1993.
107. **Saltin B, Nazar K, Costill D, Stein E, Jansson E, Essén B and Gollnick P.** The Nature of the Training Response; Peripheral and Central Adaptations to One-Legged Exercise. *Acta Physiol.Scand.* 96: 3: 289-305, 1976.
108. **Seshadri P, Iqbal N, Stern L, Williams M, Chicano KL, Daily DA, McGrory J, Gracely EJ, Rader DJ and Samaha FF.** A randomized study comparing the effects of a low-carbohydrate diet and a conventional diet on lipoprotein subfractions and C-reactive protein levels in patients with severe obesity. *Am.J.Med.* 117: 6: 398-405, 2004.
109. **Sexton WL, Korthuis RJ and Laughlin MH.** High-intensity exercise training increases vascular transport capacity of rat hindquarters. 254: 2: H274-H278, 1988.
110. **Sexton WL and Laughlin MH.** Influence of endurance exercise training on distribution of vascular adaptations in rat skeletal muscle. 266: 2: H483-H490, 1994.

111. **Shine B, De Beer F and Pepys M.** Solid phase radioimmunoassays for human C-reactive protein. *117: 1: 13-23, 1981.*
112. **Smith ML, Hudson DL, Graitzer HM and Raven PB.** Exercise training bradycardia: the role of autonomic balance. *Med.Sci.Sports Exerc.* 21: 1: 40-44, 1989.
113. **Spier SA, Laughlin MH and Delp MD.** Effects of acute and chronic exercise on vasoconstrictor responsiveness of rat abdominal aorta. *J.Appl.Physiol.* 87: 5: 1752-1757, 1999.
114. **Stamler J, Stamler R, Neaton JD, Wentworth D, Daviglius ML, Garside D, Dyer AR, Liu K and Greenland P.** Low risk-factor profile and long-term cardiovascular and noncardiovascular mortality and life expectancy. *282: 21: 2012-2018, 1999.*
115. **Stamler R, Stamler J, Riedlinger WF, Algera G and Roberts RH.** Family (parental) history and prevalence of hypertension. *241: 1: 43-46, 1979.*
116. **Steensberg A, Fischer CP, Keller C, Møller K and Pedersen BK.** IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. *285: 2: E433-E437, 2003.*
117. **Steensberg A, Febbraio MA, Osada T, Schjerling P, Van Hall G, Saltin B and Pedersen BK.** Interleukin-6 production in contracting human skeletal muscle is influenced by pre-exercise muscle glycogen content. *J.Physiol.(Lond.)* 537: 2: 633-639, 2001.
118. **Steensberg A, Van Hall G, Osada T, Sacchetti M, Saltin B and Pedersen BK.** Production of interleukin-6 in contracting human skeletal muscles can account for the exercise-induced increase in plasma interleukin-6. *J.Physiol.(Lond.)* 529: 1: 237-242, 2000.
119. **Stewart LK, Flynn MG, Campbell WW, Craig BA, Robinson JP, Timmerman KL, McFarlin BK, Coen PM and Talbert E.** The influence of exercise training on inflammatory cytokines and C-reactive protein. *Med.Sci.Sports Exerc.* 39: 10: 1714, 2007.
120. **Svetkey LP.** Management of prehypertension. *Hypertension* 45: 6: 1056-1061, 2005.

121. **Swain DP and Franklin BA.** VO₂ reserve and the minimal intensity for improving cardiorespiratory fitness. *Med.Sci.Sports Exerc.* 34: 1: 152-157, 2002.
122. **Tashiro E, Miura S, Koga M, Sasaguri M, Ideishi M, Ikeda M, Tanaka H, Shindo M and Arakawa K.** CROSSOVER COMPARISON BETWEEN THE DEPRESSOR EFFECTS OF LOW AND HIGH WORK-RATE EXERCISE IN MILD HYPERTENSION. 20: 11: 689-696, 1993.
123. **Tilg H, Dinarello CA and Mier JW.** IL-6 and APPs: anti-inflammatory and immunosuppressive mediators. *Immunol.Today* 18: 9: 428-432, 1997.
124. **Tjønnå AE, Lee SJ, Rognmo Ø, Stølen TO, Bye A, Haram PM, Loennechen JP, Al-Share QY, Skogvoll E and Slørdahl SA.** Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome. *Circulation* 118: 4: 346-354, 2008.
125. **Vaitkevicius PV, Fleg JL, Engel JH, O'Connor FC, Wright JG, Lakatta LE, Yin F and Lakatta EG.** Effects of age and aerobic capacity on arterial stiffness in healthy adults. *Circulation* 88: 4: 1456-1462, 1993.
126. **Vasan RS, Beiser A, Seshadri S, Larson MG, Kannel WB, D'Agostino RB and Levy D.** Residual lifetime risk for developing hypertension in middle-aged women and men. 287: 8: 1003-1010, 2002.
127. **Vasan RS, Larson MG, Leip EP, Kannel WB and Levy D.** Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study: a cohort study. 358: 9294: 1682-1686, 2001.
128. **Vigushin DM, Pepys MB and Hawkins PN.** Metabolic and scintigraphic studies of radioiodinated human C-reactive protein in health and disease. *J.Clin.Invest.* 91: 4: 1351, 1993.

129. **Wang C, Li S, Weisel RD, Fedak PW, Dumont AS, Szmítko P, Li R, Mickle DA and Verma S.** C-reactive protein upregulates angiotensin type 1 receptors in vascular smooth muscle. *Circulation* 107: 13: 1783-1790, 2003.
130. **Warburton DE, McKenzie DC, Haykowsky MJ, Taylor A, Shoemaker P, Ignaszewski AP and Chan SY.** Effectiveness of high-intensity interval training for the rehabilitation of patients with coronary artery disease. *Am.J.Cardiol.* 95: 9: 1080-1084, 2005.
131. **Washburn EW.** The dynamics of capillary flow. 17: 3: 273, 1921.
132. **Whelton PK, He J, Appel LJ, Cutler JA, Havas S, Kotchen TA, Roccella EJ, Stout R, Vallbona C and Winston MC.** Primary prevention of hypertension. 288: 15: 1882-1888, 2002.
133. **Whelton SP, Chin A, Xin X and He J.** Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. *Ann.Intern.Med.* 136: 7: 493, 2002.
134. **Wiegman DL, Harris PD, Joshua IG and Miller FN.** Decreased vascular sensitivity to norepinephrine following exercise training. *J.Appl.Physiol.* 51: 2: 282-287, 1981.
135. **Willerson JT and Ridker PM.** Inflammation as a cardiovascular risk factor. *Circulation* 109: 21 suppl 1: II-2-II-10, 2004.
136. **Wisløff U, Støylen A, Loennechen JP, Bruvold M, Rognum Ø, Haram PM, Tjønnå AE, Helgerud J, Slørdahl SA and Lee SJ.** Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients a randomized study. *Circulation* 115: 24: 3086-3094, 2007.
137. **Yamamoto K, Miyachi M, Saitoh T, Yoshioka A and Onodera S.** Effects of endurance training on resting and post-exercise cardiac autonomic control. *Med.Sci.Sports Exerc.* 33: 9: 1496-1502, 2001.