Comparison of Hemodynamic Responses to Acute and Chronic Exercise in Obese and Lean Prehypertensive Men

by

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ABSTRACT

PURPOSE: Lean hypertension (HTN) is characterized by a mechanistically different HTN when compared to obese HTN. The purpose of this study is to assess whether body phenotype influences blood pressure (BP) responses following both acute and chronic exercise. METHODS: Obese (body mass index (BMI) > 30 kg/m^2) and lean (BMI < 25 kg/m^2) men with pre-hypertension (PHTN) (systolic BP (SBP) 120 - 139 or diastolic BP (DBP) 80 - 89 mm Hg) were asked to participate in a two-phase trial. Phase 1 assessed differences in post-exercise hypotension between groups in response to an acute exercise bout. Phase 2 consisted of a two-week aerobic exercise intervention at 65-70% of heart rate (HR) max on a cycle ergometer. Primary outcome measures were: brachial BP, central (aortic) BP, cardiac output (CO), and systemic vascular resistance (SVR) measured acutely after one exercise session and following two weeks of training. RESULTS: There were no differences between groups for baseline resting brachial BP, central BP, age, or VO_2 peak (all $P > 0.05$). At rest, obese PHTN had greater CO compared to lean PHTN (6.3 ± 1 vs 4.7 ± 1 L/min^{-1}, $P = 0.005$) and decreased SVR compared to lean PHTN (1218 ± 263 vs 1606 ± 444 $Dyn \cdot s/cm^5$, $P = 0.003$). Average 60-minute post-exercise brachial and central SBP reduced by 3 mm Hg in Lean PHTN in response to acute exercise ($P < 0.005$), while significantly increasing 4 mm Hg for brachial and 3 mm Hg for central SBP ($P < 0.05$). SVR had a significantly greater reduction following acute exercise in lean PHTN (-223 $Dyn \cdot s/cm^5$) compared to obese PHTN (-75 $Dyn \cdot s/cm^5$, $P < 0.001$). In lean subjects chronic training reduced brachial BP by 4 mm Hg and central BP by 3 mm Hg but training had no effect on the BP's in obese subjects. Resting BP reduction in response to training was accompanied by reductions in

SVR within lean (-169 Dyn·s/cm^5, P < 0.001), while obese experienced increased SVR following training (47 Dyn·s/cm^5, P < 0.001). CONCLUSION: Hemodynamic response to both acute and chronic exercise training differ between obese and lean individuals.

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CHAPTER ONE

INTRODUCTION

Overview. According to the World Health Organization, more than a third of the world's deaths can be attributed to a small number of risk factors. Among the top five leading risk factors are hypertension (HTN), obesity and physical inactivity (233). Worldwide prevalence of HTN is roughly 1 billion individuals with approximately 7.1 million deaths worldwide being ascribed to HTN (227). While the latest guidelines addressing BP failed to comment on the category of pre-hypertension (88), the JNC 7 stated that the most vulnerable population for developing HTN are those classified as pre-hypertensive (PHTN) (108). PHTN individuals are twice as likely to develop HTN compared to normotensives (108) and are at increased risk for cardiovascular morbidity and mortality (28). However, the only recommended treatment for PHTN is lifestyle modification (28).

It is estimated that *at least* 75% of the incidence of elevated blood pressure (BP) is linked to obesity (3). Paradoxically, studies suggest that obese (BMI $\geq$ 30 kg/m^2) HTN individuals may suffer from *fewer* cardiovascular events when compared to lean (BMI < 25 kg/m^2) HTN (9, 220). It appears that the presentation of HTN may be mechanistically different between the obese and lean (133, 221). The classic characteristics of essential HTN consist of elevated *afterload* with normal cardiac output (CO) and its hemodynamic trademark is *increased* systemic vascular resistance (SVR) and contracted blood volume (133). In contrast, obese HTN individuals have been shown to have more of a *volume overload* presenting with a *decreased* SVR (221).

Most people with elevated BP respond favorably to aerobic training programs (156). In fact, the literature suggests that the greatest drop in resting BP occurs after as little as two-to-three weeks of aerobic exercise training (130, 228). However, the magnitude (and therefore clinical relevance) of BP reduction in response to exercise training varies considerably (8) and even non-responders to these programs are common (17). It is well documented that an acute exercise bout of moderate-to-vigorous intensity can result in a post-exercise hypotensive (PEH) response lasting several hours (6, 12, 23, 158). Importantly, the magnitude of one's PEH response to an acute exercise bout is a predictor of how well one may respond to a chronic exercise training program (76, 107, 120). The precise mechanisms that underlie the BP reduction in response to exercise are not completely clear (23) owing to the complex etiology of HTN and dissimilarities across heterogeneous populations. Clearly to achieve a BP reduction in response to exercise, either CO, SVR or a combination of both, must decrease. However, it is unknown how much of the variability in cardiovascular dynamics that present in response to exercise are a result of differences in body size (e.g., obese or lean).

As noted previously, obese HTN and lean HTN individuals may have a mechanistically different HTN and this may affect how they respond to acute exercise stress. For instance, during graded maximal exercise Weber et. al. (33) found that while the absolute rise in BP in response to increases in exercise intensity was similar between lean HTN and obese HTN subjects, BP rise in the lean group was more dependent on changes in catecholamine and the renin system when compared to obese (221). Moreover, the majority of studies that have assessed the BP response to exercise have only analyzed brachial BP, thereby overlooking any potential influence that central BP

and/or other hemodynamic responses may play. Central aortic BP has been shown to be an *independent* predictor of cardiovascular structural damage leading to clinical outcomes (37, 89, 106, 121, 175). In other words, variations in central pressure may provide very different information about the cardiovasculature than brachial pressure alone. For example, the CAFE (Conduit Artery Function Evaluation) study illustrated that different BP lowering drugs had similar effects on brachial BP but significantly different outcomes on central BP (229). Thus, to appropriately compare exercise effects between individuals with different body phenotype, both central and peripheral hemodynamic responses to exercise should be examined.

Purpose. There is a growing need to design exercise interventions with the goal to reduce the overall public health burden of HTN. Reductions of just 5 mmHg of SBP in the population have been estimated to result in a 14% overall reduction in mortality due to stroke, a 9% reduction in mortality due to coronary heart disease, and a 7% decrease in all-cause mortality (226). Currently, there is no published research that has examined differences in PEH or the changes in resting BP in response to acute and chronic exercise in obese and lean PHTN individuals. It is currently unknown what influence body phenotype may have on both central and peripheral hemodynamic outcomes in response to exercise. Thus, the purposes of this study are to: a) examine potential differences in the mechanisms underlying PEH and chronic resting BP changes in response to exercise in obese and lean PHTN men, and b) to determine the ability of the PEH response to predict resting BP changes following aerobic training in obese and lean PHTN persons.

Primary Aim: The primary aim of this experiment is to assess differences in CO, SVR, and changes in resting brachial and central BP between inactive PHTN obese and lean men following both acute and chronic aerobic exercise.

Hypothesis: It is hypothesized that PHTN lean and obese men will be significantly different in their central and peripheral hemodynamic response following exercise such that lean men will have a greater reduction in SVR as compared to obese men, whereas obese men will see greater reductions in CO. It is also hypothesized that the magnitude of reduction following acute and chronic exercise between groups will significantly differ with lean PHTN responding with a greater reduction in brachial and central pressure.

Secondary Aim: A secondary aim of this experiment is to assess the relationship between PEH and resting BP values following two-weeks of aerobic exercise training.

Hypothesis: It is hypothesized that the magnitude of PEH (greatest brachial SBP reduction following an acute bout of exercise) will predict the efficacy of aerobic exercise training to reduce resting SBP.

Exploratory Aim: To assess differences in measures of arterial stiffness between obese and lean PHTN men following both acute and chronic exercise training.

Hypothesis: There will be no differences in measures of arterial stiffness between groups following both acute and chronic exercise.

CHAPTER TWO

REVIEW OF LITERATURE

Hypertension Complications and Mechanisms. According to the World Health Organization, more than a third of the world's deaths can be attributed to a small number of risk factors. Among the top five leading risk factors is hypertension (HTN) (233). Worldwide prevalence of HTN is roughly 1 billion individuals with approximately 7.1 million deaths worldwide being ascribed to HTN (227). HTN has been found to be responsible for at least 45% of deaths due to cardiovascular disease and 51% of deaths due to stroke (232). Long term follow-up from the Framingham study suggest that coronary heart disease is more frequent in relation to high blood pressure (BP) than any other cardiovascular complication (38). Conversely, clinical trials have shown that the lowering of BP leads to a reduced risk for heart failure in those with elevated BP (119, 237). HTN is a contributor not only of heart disease but also stroke, kidney failure, mortality, and disability (234). There are also economic costs for HTN related interventions such as cardiac bypass surgery, carotid artery surgery, and dialysis (234).

Multiple mechanisms of HTN have been proposed, namely: higher renal perfusion pressure required for sodium excretion; impairment of renin-angiotensin system activation; increased sympathetic tone; disrupted vasodilation; and age related stiffening of central arteries (43). The kidney is a key player in the development of HTN with the prevalence of HTN ranging from approximately 22% in stage 1 to over 80% in stage 4 chronic kidney disease (CKD) (225). HTN is not only a cause but also a consequence of CKD (168), introducing a vicious circle of HTN-CKD interrelation and subsequently stronger CKD-risk association. An aging kidney is characterized by

vascular changes that decrease blood flow and glomerular filtration rate. This is also a common finding in HTN patients. In fact, it has been estimated that lifetime risk for developing HTN is 90% primarily due to the effects of the aging kidney on HTN (67).

The brain is one of the most metabolically active organs in the human body accounting for 20% of the body's resting energy consumption (186). This high energetic, and hence perfusion, demands of the brain imply that it is susceptible to ischemic injury. The Framingham study has clarified the role of HTN as a precursor to stroke (98) .

HTN poses a great deal of arterial pressure that leads to left ventricular hypertrophy (LVH) (54). In the Framingham Heart Study, the presence of LVH was associated with a 2- to 5-fold increase in myocardial infarction incidence over 30 years of follow-up (96). LVH is associated with increased morbidity and mortality independent of arterial pressure and age (54, 55). Evidence of LVH is rare in normotensive persons (114) whereas those with mild hypertension have a 2- to 3-fold risk for developing LVH and those with severe hypertension have a 10-fold increase risk for developing LVH (evidenced by electrocardiography) (97). LVH risk is evident along a full range of ventricular mass (115), with few exceptions. In athletes and healthy individuals LVH has not found to be correlated with adverse events (39, 160). Thus, in HTN, LVH appears to reflect changes in quality rather than quantity of myocardial tissue. Characteristics of LVH in HTN are cardiac myocyte hypertrophy, impairment in coronary hemodynamics, and ventricular fibrosis.

HTN has also been shown to correlate with left atrial enlargement, decreased atrial contractile function and increase risk of atrial fibrillation (8). Atrial systole

contributes up to 40% of diastolic filling and atrial fibrillation can precipitate overt heart failure in patients with underlying ventricular diastolic dysfunction (183).

In HTN, coronary blood flow is usually maintained but coronary vascular resistance is increased (126). Numerous reports have also shown that the ability of the vasculature of a HTN person to dilate in response to stimuli is reduced (126). For example, subjects with HTN and LVH may have *exercise induced* systolic dysfunction, even though left ventricular systolic function is normal at rest (189). This appears to be one of the dominant effects that HTN has on the vasculature, its inability to enlarge in response to increased flow. This is more than likely due to arterial structural and functional remodeling that occurs with HTN (33). Increased growth of the media in the arterioles, primarily due to smooth muscle hyperplasia, leads to increased vascular resistance.

Another feature of HTN is myocardial fibrosis. Myocardial fibrosis limits coronary perfusion by restricting vasodilation and interfering with relaxation and thus diastolic function (179). This impaired relaxation further limits myocardial perfusion.

Functional changes in the arterial tree also accompany HTN, most notable are the effects on endothelial function (41, 201). The major factor impacting endothelial function is diminished nitric oxide and other vasodilators and increased endothelium derived vasoconstrictors. Impaired endothelial function provides an important pathophysiological mechanism to HTN related complications.

Coronary circulation is affected early in the development of HTN heart disease. Impairment in coronary flow reserve and an increase in vascular resistance have been found in asymptomatic borderline hypertensive patients with no evidence of LVH (153).

Over time the development of LVH and structural remodeling occurs which leads to increased impairment in coronary circulation.

Another characteristic of HTN is increased collagen accumulation in myocardial tissue (219). The mechanisms for the collagen accumulation is not completely understood but is thought to be partially explained by the renin-angiotensin aldosterone system and salt intake (55, 219). Animal studies have shown that increased levels of angiotensin II or aldosterone develop LVH and fibrosis independent of arterial pressure (218, 219).

Prehypertension. Risk of high BP need not be relegated to only those of the HTN status. Indeed, early population based studies have shown an impact of minor BP elevation on the risk of coronary disease (161, 192). In 1939 Robinson and Bruce found that SBP in the range of 120-140 mm Hg was associated with high risk of progression to HTN and cardiovascular disease later in life (169). They referred to those in this BP category as prehypertensive (PHTN) (169). In 2003, The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) incorporated the term "prehypertension" into the guidelines and defined it as resting systolic BP values of 120-139 mm Hg *or* diastolic BP of 80-89 mm Hg (28). The latest JNC-8 did not address the use of the term or category of PHTN (88). The NHANES III reported that the prevalence of PHTN is 31% while men experience an increased risk for PHTN compared to woman (40% compared to 23%) (215).

Two landmark studies were integral in the development of this BP category. A meta-analysis of approximately one million people from 61 epidemiological studies showed that mortality from ischemic heart disease and stroke in those aged 40-89 yr

increases linearly with both systolic BP and DBP (116). Starting at a BP of 115/75 mm Hg there is a two-fold increase mortality risk for every 20 mm Hg increase in SBP and 10 mm Hg increase in DBP (116). Secondly, longitudinal data from the Framingham Heart Study showed that people with BP values in the PHTN range compared to those with values considered normal (less than 120/80 mm Hg) are at increased risk for developing HTN and cardiovascular disease later in life (209).

The use of the term, "prehypertension", has been somewhat contentious. In the 2013 report from the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension and the European Society of Cardiology, preference was to classify 120-129/80-84 mm Hg as normal and 130-139/85-89 mm Hg as "high normal"(123). The argument for this is that the risk for cardiovascular disease is different in those with BP on the lower ends of the PHTN category compared to the higher ends. A 2013 meta-analysis showed that PHTN was associated with significantly increased risk of coronary heart disease when compared to those within normal range (relative risk of 1.36) (185). However, when separating the individuals into either high PHTN or low PHTN groups, only the high PHTN group showed increase risk for coronary heart disease (185). On the other hand, a separate meta-analysis reported that even for low-range PHTN, risk of cardiovascular disease was significantly higher than for optimal BP and further increased with high range PHTN (82).

A 2014 meta-analysis examined PHTN and the risk of all-cause mortality, cardiovascular disease, coronary heart disease, and stroke (79). Fifty articles including data on 1,129,098 subjects were included in the analysis. After adjusting for multiple cardiovascular risk factors, PHTN subjects had a relative risk (RR) of 1.28 for

cardiovascular mortality, 1.12 for coronary heart disease, and 1.41 for stroke mortality compared to those who fell within the normal BP range. PHTN was not associated with all-cause mortality.

Cross-sectional studies have shown that PHTN, particularly high range, is associated with CKD and end-stage renal disease (ESRD) (36, 105, 235, 236). Cross-sectional data is problematic in this case particular because renal dysfunction can provoke raises in BP. A 2014 meta-analysis reviewed 22 prospective cohort studies that included data from 1,003,793 participants to assess the risk of ESRD among those classified as PHTN (80). Overall, PHTN was associated with increased risk of ESRD (RR, 1.59). Even when splitting the group into low PHTN and high PHTN, low PHTN participants still exhibited increased risk of ESRD when compared to those with optimal BP (RR, 1.44). This risk increased to 2.02 when examining subjects in the high PHTN group.

Recent work demonstrating the clinical significance of the PHTN category comes from the Systolic Blood Pressure Intervention Trial (SPRINT). Approximately 10,000 HTN individuals over the age of 50 were randomized to either a BP goal of < 140 mm Hg or a more intensive goal of < 120 mm Hg. Subjects in the conservative goal group received an average of two separate antihypertensive medications compared to three medications for those in the more intensive group. Compared to the high BP goal, subjects in the lower BP group saw a reduction of myocardial infarction, acute coronary syndrome, stroke, heart failure, or cardiovascular death by 30% and the mortality risk decreased by almost 25% (145).

Ample research show that those in the PHTN category are at increased risk for risk for stroke (83), coronary heart disease (185), ESRD (80), cognitive impairment (27,

46) and cardiovascular morbidity and mortality (81). Prehypertensive individuals are also the most vulnerable population for developing HTN (108). Indeed, PHTN individuals are twice as likely to develop HTN compared to normotensives (108). Owing to this, some have even suggested that drug therapy be initiated within the PHTN group to stave off risk (57). However, the only universal recommended treatment for PHTN is lifestyle modification (28).

Blood Pressure Regulation. Components of peripheral BP regulation can be illustrated by using the following equation, Mean arterial pressure = Cardiac Output (CO) X Systemic Vascular Resistance (SVR). Therefore, anything impacting either one of these variables will impact BP. BP is a somewhat tightly regulated variable in the sense that baroreceptors located in areas such as the aortic arch and carotid sinus mechanically deform with changes of BP. These variations will then evoke afferent nerve signals that integrate in the brain stem cardiovascular centers causing adjustments in heart rate (HR) and efferent sympathetic activity. These adjustments will then regulate CO and SVR.

Regulation of BP is not quite as simple however when examining the numerous variables that impact SVR and CO. For example, assuming an upright posture elicits a reduction of venous return causing a decreased CO (25). During heat stress cutaneous vasodilation causes both a reduction in SVR and venous return, contributing to a fall in systemic BP (34). Long-term changes in blood volume can also play a significant effect on BP control via CO. If blood volume and pressure are low, sodium and water retention are increased and if blood volume is high there can be natriuresis and diuresis (33). The aforementioned mechanism is thought to be inappropriately activated in HTN so that blood volume and BP are maintained at higher levels. In this context antihypertensive

drugs such as diuretics target blood volume or elements of the renin-angiotensin-aldosterone axis. Lastly, there are marked inter-individual age and sex differences in sympathetic vasoconstrictor responsiveness. For example, elderly men have higher baseline levels of muscle sympathetic nerve activity than young men and they also vasoconstrict less to a given ά-adrenergic stimulation (181). In addition, in young men there is a tight relationship between baseline muscle sympathetic nerve activity that is not seen with young woman (75).

We also know that BP shows great variability throughout the day in healthy, normotensive individuals. BP is typically the highest in the morning hours and the lowest around the hours of 3 pm with about a 30% variation throughout the day (136).

Many factors affect BP regulation and much heterogeneity in the pathophysiology of hypertension exists. In fact, individuals who share a similar BP value may not necessarily share similar risks of cardiovascular events owing to different pathophysiology. This has been documented when examining the physiology of obese compared to lean HTN individuals.

Obesity and Blood Pressure. Large population based studies have long since established BMI as a risk factor for developing HTN (58), with waist circumference and waist to hip ratio being more strongly related to HTN (113). There are many proposed mechanisms linking obesity to HTN. Adipose tissue dysfunction for example, is associated with overweight and obesity (66). Dysfunctional adipose tissue in obesity is characterized by hypertrophied adipocytes and changes in secretion of adipokines (66). Clinically this is important as decreased levels of adiponectin may provide a direct link between obesity and HTN. Adiponectin is an important stimulator of endothelial nitric

oxide synthase, playing a critical role in controlling vascular tone, inflammation, and smooth muscle cell proliferation (216). Adiponectin levels are also independently associated with vasomotor dysfunction and thus peripheral vascular resistance (152).

Obesity induces sympathetic nervous system (SNS) activation (61), which in turn may elevate BP by causing peripheral vasoconstriction and impaired pressure natriuresis. Leptin, another adipokine, causes reduction in appetite and an increase in SNS activity. Obesity is associated with elevated leptin levels but a blunted responsiveness to the anorexic effects (144), while sympathetic outflow to kidneys and peripheral vasculature is still preserved (163). When infused into animals, leptin raises BP (184), stimulates the SNS (44), and has been shown to correlate with BP in a few human studies (2, 102).

Overweight and obesity, particularly abdominal obesity, are also associated with increased systemic inflammation and oxidative stress (162), both of which are associated with arterial stiffness and HTN (180), possibly mediated by endothelial dysfunction (191).

Obesity has also been shown to increase renal sodium reabsorption (68, 69) possibly because of heightened sympathetic renal activity (173). In turn, this could help explain the increased plasma volume and CO found in obese individuals (56). It has been found that serum levels of almost all components of the renin angiotensin aldosterone system (RAAS) are elevated in obesity (48, 60, 204). Although RAAS hormones are predominately produced elsewhere, adipose tissue has been shown to be an important source of RAAS components (48). In the Framingham Offspring Study, aldosterone was positively correlated with both the development of the metabolic syndrome and increased

SBP (86). Sodium aldosterone has also been found to promote sodium retention, inflammation, oxidative stress, and insulin resistance (31).

Comparison Between Obese and Lean Hypertension. Essential HTN is characterized by a normal CO, enhanced contractility, and an elevated afterload with its hemodynamic trademark being an elevated vascular resistance (133). In contrast, in obese patients SVR has been found to be decreased and total blood volume expanded. Thus, with regard to SVR and total blood volume, the effects of obesity and HTN directly offset each other and these hemodynamic measures may be found within normal limits in obese persons with essential HTN (131).

A distinguishing difference between obese and lean HTN is the effect of body weight on left ventricular hypertrophy (LVH). Obesity is characterized by an accumulation of excessive amounts of adipose tissue, which in turn increases total body oxygen consumption, thus requiring an increase in CO (131). Because HR remains unchanged, the elevated CO is a result from increased stroke volume (SV). An expanded SV dictates an elevated left ventricular end diastolic volume and filling pressure. As a consequence, the left ventricle reacts with dilatation and an increased systolic and diastolic diameter. Chamber dilatation increases wall stress and therefore afterload. The left ventricle adapts to this burden by increasing its muscle mass. However, this increased muscle mass remains proportional to the increase in chamber volume. Indeed, the radius/wall thickness ratio has been documented to remain unchanged in obesity, indicating eccentric hypertrophy (111, 112, 231).

Typically, HTN leads to increasing afterload and this leads to thickening of ventricular walls without chamber dilation, or concentric hypertrophy (131). Systolic

pressure is a known determinant of left ventricular mass (178) and correlate inversely with the radius/wall thickness ratio in lean subjects. In contrast, obesity is associated with left ventricular dilatation and proportional increase in wall thickness (132). Therefore, eccentric hypertrophy results and may override the effects of a patient who is HTN and overweight. Both disease entities increase left ventricular stroke work (obesity by increasing SV and arterial HTN by the increase in systolic pressure), the mechanisms however differ. This mechanistic difference between lean and obese HTN has been speculated as a possible reason for the obesity paradox seen in relation to obesity, elevated BP, and CV mortality.

Obesity Paradox. High BP is the leading risk factor for CVD throughout the world (117). In fact, According to the Global Burden of Disease Study, BP and BMI combined account for > 60% of the global burden of CVD (50). These two risk factors frequently coexist due, in part, to a causal positive relationship between BMI and BP. The prevalence of HTN among the obese is 42.5%, compared to 15.3% among non-obese (215). Investigations purport excess weight gain accounts for 60-70% of essential HTN (143). Studies have shown that a gain in BMI of 2.1/2.7 $kg.m^2$ (men/woman) is associated with a 2.2 mm Hg increment in SBP (22), and likewise a weight loss of 1 kg results in a 1 mm Hg reduction in BP (147). There is some evidence that the magnitude of the association between BP and subsequent cardiovascular disease or stroke is stronger in obese, compared to lean individuals (187). However, disagreement and controversy exists in the literature as to the role that BMI may or may not have on mitigating the deleterious effects of elevated BP (187, 202). Paradoxically, studies suggest obese HTN individuals may suffer from *fewer* cardiovascular events when compared to their lean

HTN counterparts (91, 100, 135, 220). This paradox between obese and lean HTN individuals may be explained by the divergent pathogenesis between lean and obese individuals (29, 42, 95).

Early cohort studies suggest that BMI modifies the relationship between BP and subsequent risk of coronary heart disease, that is, the relationship between BP and vascular risk is diminished with increasing BMI (9, 21, 24, 47, 59, 193, 202). Subsequent cohorts however have produced inconsistent reports (159, 187) and one study of young males reported a synergistic effect of BMI on the relationship between BP and cardiovascular disease risk (187). Other studies have reported a U-shaped relationship between all-cause, cardiovascular, and non-cardiovascular mortality and BMI, meaning excess mortality at both extremes of BMI (193, 203). Other studies have reported no interaction of any sort on BMI, BP, and cardiovascular disease (15, 99, 159).

In addition to cardiovascular disease, greater risk among lean HTN persons compared with obese HTN has also been reported for total mortality (11, 129, 205, 217). Uretsky et al. (205) investigated the effects of obesity on cardiovascular outcomes in 22,576 treated HTN patients with known coronary heart disease. During a 2-year follow-up, all-cause mortality was 30% lower in overweight and obese patients, despite less effective BP control in these patients compared with the normal weight group. Some have postulated that confounding factors such as smoking (smokers tend to have a lower BMI) could distort the relationship between BMI, mortality, and BP. However, in studies that control for smoking, excess coronary heart disease risk among lean HTN is still present (202).

To further illustrate the clinical differences between obese and lean HTN individuals, pharmacological treatment variations between BMI groups are addressed. Choice of treatment to control BP is typically made without regard to differences in body weight between patients. Yet, recognition of clinical and prognostic differences between weight categories could affect selection of treatment. The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial has allowed a further look into this hypothesis. The ACCOMPLISH trial was a multicenter trial undertaken at 548 academic centers in the USA, Sweden, Norway, Denmark, and Finland. The purpose of the trial was to compare the effects of a combination of an angiotensin-converting enzyme (ACE) inhibitor and a calcium channel blocker with the effect of a combination of the same ACE inhibitor with a thiazide diuretic. The primary endpoint was a reduction of cardiac and stroke events in HTN patients. This particular investigation was conducted as a secondary analysis to provide insights into the differential effects of treatment on cardiovascular events in HTN patients categorized by BMI (220). Approximately 11,000 individuals were randomized to either the ACE inhibitor and calcium channel blocker or the ACE inhibitor and the diuretic. There was a significant difference between weight groups (normal, overweight, obese) on the number of cardiovascular events with 7% of patients in the normal weight, 6% in the overweight, and 5% in the obese group reaching the primary endpoint ($P = 0.025$). Post hoc analysis revealed that the difference occurred between the obese and normal weight groups ($P = 0.006$). It was also found that there was a significant difference between treatment arms for the normal weight (43% risk reduction; $P = 0.003$) and overweight group (24% risk reduction; $P = 0.037$) in favor of the ACE inhibitor and

calcium channel blocker. These findings indicate two important points; first, cardiovascular deaths or non-fatal myocardial infarctions or strokes happen more frequently in normal weight than obese HTN patients, and secondly, the type of treatment to which patients were randomly allocated were determinants of relations between body mass and cardiovascular outcomes.

Not all studies coincide with the previous findings. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) (165) showed a reduction in risk of cardiovascular events across the full range of BMI with the use of perindopril with no evidence to support an interaction between BMI and the effect of BP lowering. A 2015 review of literature assessed the effects of different BP lowering drugs according to baseline BMI (14). Twenty-two randomized controlled trials that included a total of 130,000 individuals were included in this review. The purpose of this analysis was to assess if different treatment regimens (pharmacological) between BMI groups favored different BMI classes. This particular analysis did not convincingly show that a particular drug class was more or less effective among patients with different BMIs. There was a small additional benefit for individuals with higher BMI with ACE inhibitors. This greater protection with ACE inhibitors in obese possibly could be explained on the basis of the upregulated state of the RAAS in obesity-mediated hypertension (42, 95). Indeed, ample pharmacological literature indicates that drug effectiveness is impacted by a patient's body weight status, indicating a different type of HTN between body phenotype.

Exercise Response in Obese and Lean. In addition to different pharmacological treatment outcomes between obese and lean HTN, there may be divergent outcomes from

physical stress. In 2001 Weber et al sought to address the question as whether obese and lean HTN subjects could be differentiated by their response to a standardized treadmill protocol (221). The hypothesis was that differences in catecholamine and renin values might discriminate between obese and lean HTN and that treadmill testing might reveal properties that could give further insight to explain differences in the clinical outcomes seen between obese and lean HTN individuals. 121 male and female subjects were classified into either obese (BMI> 30 kg/m^2) HTN, lean (BMI < 25kg/m^2) HTN, obese normal BP, lean normal BP. The groups were matched for age and BP. Baseline blood samples were taken for insulin, plasma renin activity, and catecholamines. In addition, renin and catecholamine samples were drawn before and immediately after exercise. Baseline echocardiographic studies were also measured on all subjects. Every subject underwent a full treadmill test according to the Balke-Ware treadmill protocol (230). There were no baseline differences in renin or catecholamine values and there was no difference between groups on left ventricular mass index. However, assuming a standing posture caused a greater increase in norepinephrine in the lean HTN subjects compared to the obese HTN subjects. During the exercise test there was no difference on the maximal BP value between groups. During exercise there was a greater rise in plasma norepinephrine and renin activity in the lean HTN group compared to the obese group. It was also shown that at baseline the lean HTN group showed signs of greater arterial hardening via the SV/pulse pressure ratio. This study further adds to what has been known and that is that obese and lean HTN are two distinct conditions (166).

Rockstroth Schmieder, Schachinger, and Messerli (170) also looked at the stress response differences between lean and obese HTN individuals using both a mental stress

and isometric handgrip exercise. Subjects with a BMI > 27 kg/m^2 were considered obese and BMI < 27 kg/m^2 were considered lean. Two stress tests were conducted, first was a mental stress test. Subjects were asked to do basic math while being timed and distracted by a metronome in the background. The second test had the subjects perform isometric handgrip at one third of maximal contraction for over three minutes. At baseline and during both assessments, measurements of HR, BP, SV, CO, and SVR were measured. During mental stress the obese group was characterized by a slightly higher increase in DBP and a significantly increased peak DBP when compared to lean ($p < 0.02$). The hemodynamic profile in lean HTN during mental stress was characterized by a decrease SVR. In contrast obese was characterized by increase SVR ($p <0.03$). The lean HTN subjects saw pronounced increases in CO, HR, and SV. The obese subjects exhibited blunted increase in CO and HR ($P < 0.05$). Thus in obese HTN, mental stress caused an exaggerated increase in SVR and conversely attenuated increase in CO resulting in an elevated peak DBP. The isometric exercise induced a more pronounced increase in SBP and DBP in the obese compared to the lean group ($P < 0.05$). During isometric stress, obese HTN was also characterized by significantly greater increase in SVR compared to the lean HTN group.

It has been known that mental and isometric stress increase BP in both normal and HTN individuals. The mechanisms between the stressors to this BP elevation are different. Mental stress has been shown to cause an increase in CO and HR and a decrease in SVR, resulting predominately from epinephrine (63). In contrast, isometric stress is determined by the release of epinephrine and norepinephrine, leading to an increase in HR and CO with no change or a slight increase in SVR (118). Taken

together, obesity seems to modify the hemodynamic pattern of response to mental and isometric stress: with mental stress, vasoconstriction rather than vasodilation is seen, whereas with isometric stress, the response in BP becomes more exaggerated in obese HTN than in lean HTN.

Central Blood Pressure and Central Arterial Stiffness. For fifty years it has been known that end-diastolic BP is nearly identical throughout the arterial tree while SBP varies among arterial segments because of arterial pulse pressure amplification (74, 172, 177). The result of this is a higher brachial SBP compared to central aortic SBP (101). Accordingly, measuring SBP at the brachial artery and assuming transferable pressure values in the central circulation is erroneous. Brachial BP is the product of CO and SVR, central BP is more complex and is affected by arterial stiffness and the timing and magnitude of the pressure wave (87, 151). Aortic systolic pressure is determined by both cardiac factors (SV and ejection time) and arterial factors (arterial stiffness and pulse wave reflection).

Growing evidence from epidemiological (171, 214) and clinical observation (90) suggest that central BP may be more relevant than peripheral BP in predicting target organ damage and cardiovascular outcomes. The population-based Strong Heart Study examined 3520 American Indians and found that central pulse pressure was the best predictor of common carotid artery and intimal-medial thickness (171). Similar findings have been reported in other population-based studies conducted with Taiwanese (214) and South African individuals (148). In addition to intimal-medial thickness, the population-based Taiwanese study (214), Strong Heart Study (171) and the European InGenious HyperCar study (146) showed that central SBP was more strongly related to

LV mass than brachial SBP. Waddell et al examined the effect of central pressure on its ability to predict coronary artery disease. 114 men were divided into two groups; i) moderate (50% to 89% stenosis) or ii) severe (> 90% stenosis). Carotid SBP, but not brachial pressures were independent correlates of percent coronary artery narrowing ($r = 0.47$; $P < 0.001$) (213).

Additionally, some drug therapies have been shown to affect brachial BP and central BP/hemodynamic properties differently (229). Thus highlighting the importance of knowing both brachial and central BP. The closer relation of central BP to preclinical cardiac and vascular disease is because the loading conditions of the heart and coronary vessels are better represented with the central pressure. Indeed, important information is neglected when measuring BP at only the brachial artery with the sphygmomanometric method.

Pulse wave velocity (PWV) has emerged as a valuable tool in the assessment of aortic stiffness. Arterial stiffness increases as elastic fibers in the lamina media of the aorta are destroyed and replaced by collagen fibers (109) resulting in an increase in aortic impedance and PWV (127). The properties of the arterial wall, its thickness, and arterial lumen diameter are the major factors influencing PWV (174). The Framingham Heart Study showed that aortic stiffness, measured as carotid-femoral pulse wave velocity (cfPWV) was superior to brachial arterial stiffness, augmentation index, central pulse pressure, and pulse pressure amplification on predicting cardiovascular events (137). Central femoral PWV is now considered the gold standard for measuring arterial stiffness (110). The 2007 guidelines on the management of arterial hypertension state that the

relationship between arterial stiffness and events is continuous, however a threshold of 12 m/s has been proposed (124).

Pulse wave analysis (PWA) is the assessment of the augmentation index (Aix), which is an indirect measure of arterial stiffness that assesses pulse wave reflection and calculates how much of the central pressure is accounted for by the reflected wave pulse. This can also be expressed in absolute terms as the augmentation pressure (AP). Although PWV and Aix are correlated, they are two different measurements of the properties of the arterial tree that cannot be used interchangeably (149). Aix has not been as extensively studied as PWV but has been found to be related to known risk factors of CVD (207) and is significantly correlated to the degree of coronary artery disease (222).

The gold standard for assessing central hemodynamics would be to measure directly. However, this is extremely invasive, therefore, several validated methods using applanated carotid or radial pulse distension waves have been presented. The SphygmoCor MM3 (ArCor Medical) is a well-validated (1, 154) and extensively used system to measure central hemodynamics. The newer XCEL^{TM} device has also been shown valid and reliable (84) and uses a simpler, more convenient approach to measure arterial stiffness and wave reflection characteristics.

Using the SphygmoCor XCEL^{TM}, PWA can be captured by deriving an ascending aortic pressure waveform from the brachial artery waveforms recorded at the arm, using a specialized cuff containing a high-fidelity micromanometer. After 10 sequential, high-quality waveforms (software derived from an algorithm including average pulse height, pulse height variation, diastolic variation, and the maximum rate of rise of the peripheral waveform) are acquired, a validated generalized transfer function is used to generate the

corresponding central aortic pressure waveform. AIx is influenced by HR, due to this, an index normalized for a HR of 75 beats/minute (AIx at HR75) is typically used.

Carotid-femoral pulse wave velocity (cfPWV) can also be determined by using the SphygmoCor XCEL^{TM}. The cfPWV is measured by simultaneously recording carotid artery wave forms by applanation tonometry and femoral artery waveforms using a specialized micromanometer equipped cuff. Distances from the carotid sampling site to the suprasternal notch and from the suprasternal notch to the femoral cuff are measured as straight lines between the points on the body surface using a tape measure. The distance from the femoral arterial pulse to the femoral cuff is obtained and subtracted from the total distance (D). The time (t) between the onset of femoral and carotid waveforms is determined as the mean from 10 consecutive cardiac cycles. The cfPWV is calculated from the distance between measurement points and the time delay (t) as follows: PWV = D/t (m/sec), where D is distance in meters and t is the time interval in seconds.

Endothelial function. It is now understood that central arterial stiffness *precedes* the development of hypertension (94, 223). Arterial stiffness is greater in the obese than in the lean and obese individuals are more likely to have increased aortic stiffness independent of BP levels, ethnicity, and age (176). However, arterial stiffness may not be linked to obesity per se, but specifically to central adiposity (51, 52). The physiopathology of this is not completely understood, but it is known that visceral adipocytes have elevated lipolytic activity resulting in increased free fatty acids released into the portal vein contributing to insulin resistance (176). Other hypotheses focus on increased circulating proinflammatory cytokines or leptin (188, 210). Leptin has been

shown to exert receptor-mediated influence on vessel tone and growth and, in cell culture, stimulate vascular smooth muscle proliferation and migration (150). Another factor proposed to explain increased stiffness in abdominal obesity is nitrite oxide (NO) disturbance (176). Endothelial dysfunction is characterized by a reduced bioavailability of endothelium derived NO and has been found to be associated with arterial stiffness (128).

The gaseous mediator NO plays a key role in protection against cardiovascular disease. NO is produced when L-arginine is transformed to L-citrulline via the catalysis of eNOS. Endothelial eNOS eventually is activated for NO synthesis. NO prevents abnormal constriction of the coronary arteries, inhibits aggregation of platelets, the expression of adhesion molecules, and the adhesion and penetration macrophages (208). When NO availability is hampered, the inflammatory response (49) that may lead to atherosclerosis is set into motion (212). Both acute and chronic increases in shear stress exerted on the arterial wall augment the release of NO (20). The acute effect of this increased shear stress on NO release stimulates Flow-Mediated Dilation (FMD), a response used in humans to estimate the functional state of the endothelium. FMD is a non-invasive measurement of endothelial function and correlates closely with the gold standard intra-coronary or intra-brachial infusions of vasoactive agents (4, 200). The chronic effect of shear stress on the endothelium explains the beneficial effects of exercise on endothelial function (35).

Endothelium-dependent vasodilation has been found to be blunted in hypertensive humans and probably reflects the premature aging of the vasculature being chronically exposed to increased arterial BP (208). Other factors affecting endothelial dysfunction in

obesity may be explained by adipokine dysfunction (199). As with central hemodynamics, of greater importance than total body fat, is abdominal obesity. It has been shown that in healthy overweight adults an increased waist- to-hip ratio is a strong predictor of vascular endothelial dysfunction, independent of other cardiovascular risk factors (18). Insulin resistance has been identified as a pathogenic mechanism for the development of endothelial dysfunction (103, 194). In fact, obesity in the absence of insulin resistance has not been found to cause endothelial dysfunction (45).

It is generally recognized that endothelial dysfunction is the first step leading to arteriosclerosis (139, 208). The prognostic value of brachial FMD on cardiovascular events and all-cause mortality, that is FMD is an independent predictor of CV events and all-cause mortality, have been demonstrated in three meta-analyses (85, 164, 195). Indeed, just a 1% increase in FMD showed a relative risk of future cardiovascular events of 0.872 (85).

Aerobic Training and Cardiovascular Outcomes. Most people with elevated BP respond favorably to aerobic training programs (156). Aerobic exercise training has been shown to reduce resting BP 5 – 7 mm Hg among those with HTN (197). This magnitude of reduction rival's decreases obtained from first line antihypertensive medications and lowers heart disease risk by 20-30% (88). In fact, the literature suggests that the greatest drop in resting BP occurs after as little as one-to-three weeks of aerobic exercise training with no further decrease thereafter (130, 142, 228). Because of this, aerobic exercise is encouraged by many national health organizations including the American College of Sports medicine who advocate moderate intensity aerobic exercise for 30 – 60 min or more on most, preferably all, days of the week to lower BP (157).

However, the magnitude (and therefore clinical relevance) of BP reduction in response to exercise training varies considerably (8) and even non-responders, upwards of 25%, to these programs are common (17). Bouchard et al. consolidated data from six large exercise studies and found that 12% of the sample actually *increased* BP (> 10 mm Hg) in response to exercise training (16). These data illustrate the critical need to identify factors that explain the heterogeneity of exercise response on BP. Few predictors have been explored such as, initial resting BP (those with higher BP will see greater reductions), magnitude of PEH (77, 107, 120), BP response to de-training (138) and presence or absence of the metabolic syndrome, those without the metabolic syndrome respond better (155).

The precise mechanisms that underlie the BP reduction in response to exercise are not completely clear (23) owing to the complex etiology of hypertension and dissimilarities across heterogeneous populations. Clearly to achieve a peripheral BP reduction in response to exercise, either CO, SVR or a combination of both, must decrease. However, it is unknown how much of the variability in cardiovascular dynamics that present in response to exercise are a result of differences in body size phenotype (e.g., obese or lean).

Studies examining the effects of exercise on endothelial function are equivocal, more than likely due to various duration of exercise protocols. Short term aerobic exercise training has been shown to enhance eNOS and NO bioactivity (40) while long term training induces structural adaptations resulting in an increased arterial size (19). It has been proposed that long term training studies fail to capture functional changes, via FMD, because structural adaptations occur, normalizing shear rate levels causing

endothelial function to return to normal levels. Tinken et al had 20 men exercise for 8 weeks while measuring FMD every two-weeks (198). It was found that exercise-induced functional changes in conduit arteries precede structural adaptations and that brachial artery endothelial function initially increased in response to exercise training while peaking after two-weeks (6 sessions) of training.

Generally speaking, exercise training in those with known risk factors of CVD has been found to increase endothelial function, while exercise training in healthy subjects with normal endothelial function does not provoke changes to the endothelium (62). Beneficial changes on the vascular endothelium are thought to be caused by exercise increased NO-synthase protein expression and phosphorylation (73).

A 2014 meta-analysis (7) examining the effect of different exercise training modalities on arterial stiffness found that aerobic exercise significantly reduced PWV by -0.63 m/s. Additionally, they established that aerobic training caused greater reductions in peripheral arteries (brachial-ankle PWV) in comparison with central arteries (cf-PWV) and those with stiffer arteries (PWV >8 m/s) saw greater reductions in PWV. In addition, training that lasted longer than 10-weeks showed the best benefit on PWV. It has been shown that every 1 m/s increase in PWV is associated with a 12-14% increase risk of CV events and 13-15% increase risk of CVD mortality (211). The 0.63 m/s decrease seen from aerobic training could lead to an 8% reduction in CV events and a 9% reduction in CV mortality. In addition to PWV, it was concluded that aerobic exercise training significantly lowered Aix by 2.63%. Interestingly they found that exercise intensity rather than volume was positively associated with improvement in Aix. This analysis

included only randomized controlled trials and included studies with subjects classified as obese, prehypertensive, hypertensive, diabetic, and chronic kidney disease.

In contrast, other meta-analyses failed to find positive effects of aerobic exercise on arterial stiffness in prehypertensive, HTN (141), and obese (140) participants unless associated with reductions in SBP. These two studies included non-randomized controlled trials into their analysis, possibly explaining the differing conclusions.

Acute Exercise and Blood Pressure. It is well documented that an acute exercise bout of moderate-to-vigorous intensity can result in a post-exercise hypotensive (PEH) response lasting several hours (12, 23, 70, 122, 158) with the greatest fall in BP occurring within the first hour following (5, 77).

Taylor-Tolbert et al. (196) recruited 11 sedentary obese hypertensive subjects to examine the duration of BP reduction after an acute bout of aerobic exercise. The study was a crossover design in which all subjects performed a control day and an exercise day. Exercise consisted of 45 min of aerobic exercise at 70% VO2 peak. Ambulatory BP was recorded for 24-h after exercise and on a separate non-exercise day for the control. It was found that SBP was lower by 6 to 13 mm Hg for the first 16 h after exercise when compared to the control day. Significant reductions were also seen in DBP 16 hours and over the course of the 24 h after exercise. It was concluded that a single bout of moderate intensity aerobic exercise significantly lowered BP in obese sedentary hypertensive men.

PEH is consistently witnessed in HTN and PHTN subjects with varying findings in normotensive populations (122). However, it has been suggested that differences between normotensive and hypertensives more than likely reflect quantitative rather than qualitative differences (70).

Most literature suggest that exercise intensity is not a critical factor on PEH (53). Nonetheless, a recent article published in 2015 showed that aerobic interval exercise (four 4-minute intervals at 90% HR max separated by 3 min recovery) was superior to steady state exercise (70-75% HR max) and anaerobic sprint interval exercise (30-second Wingate) on both magnitude and duration of PEH (5). High intensity exercise may be superior to lower intensities on provoking PEH. Nevertheless, the other end of intensity spectrum has documented extremely low activities such as standing (238) and walking at 1 mph (239) lowering ambulatory BP when compared to a non-activity seated day.

Importantly, the magnitude of one's PEH response to an acute exercise bout is a predictor of how well one may respond to a chronic exercise training program (76, 107, 120). This is imperative as it has been identified that as many as 25% of people with elevated BP do not see BP reductions following endurance training (65). Applying this relationship may help identify "non-responders" to chronic exercise. A paper published in 2012 by Liu and colleagues (120) and another in 2013 by Hecksteden (77) first showed this relationship between PEH and chronic endurance training in small groups of prehypertensive individuals. The magnitude of PEH was strongly correlated with change in resting BP values ($r=0.89$ $p< 0.001$, $r = 0.75$ $p < 0.001$, respectively, data derived from (120)). A 2015 paper replicated the same study question with an increased sample size ($n = 116$) and a population with coronary artery disease (107). Similar results were found in relation to SBP but there was not a significant association between diastolic PEH and chronic training response. A weakness of all three studies were that there were no measurements into possible mechanism responsible for the PEH such as systemic vascular resistance, arterial stiffness, and endothelial function.

Fractionized exercise has shown superior to one bout of exercise at eliciting PEH (6, 12, 224). Weltman et al. (224) examined the BP response to fractionalized (three bouts separated by time) exercise compared to a single session. Sedentary normotensive to prehypertensive adults were enrolled in the study. Participants were randomly assigned to either a 1 x 30-minute session or 3 x 10-minute session at a VO_2peak of 60-70%. The 1 x 30-minute exercise session was performed from 0900-0930; the 3 x 10-minute sessions were initiated at 0920, 1320, and 1720 hours. All subjects performed both sessions in addition to a control day. BP was taken hourly from 0900 to 2100 hours by an automated cuff. Between readings the subjects were at bed rest. It was found that when compared to the control and the 1 x 30 day, fractionalized exercise had consistently lower SBP in the afternoon and early evenings. Authors concluded that repeated exercise bouts may be superior to one exercise bout to reduce SBP in those with slightly elevated BP. PEH was not observed in the 1x 30 group. This is thought to be due to inconsistent findings of PEH within the normotensive population and the timing of the exercise (122). Exercise in the afternoon has been found to have a stronger effect on PEH than exercise in the morning (93).

Mean arterial pressure is the product of CO and SVR. In the majority of cases, indices of systemic and regional resistance are reduced below pre-exercise values during the hypotensive period (122). Conversely, CO is most often elevated during PEH (71). However, in different populations this may not be the case. It has been shown in elderly men that post exercise peripheral resistance may actually be increased (64). Also, in endurance trained men CO has shown to decrease below pre-exercise values but not in woman (182). Except in endurance trained men (182), stroke volume remains unchanged

during the PEH period following exercise (72). This leads to the understanding that the mechanisms for PEH are different in heterogeneous populations. Mechanisms of PEH in differing populations warrant further investigation as divergent mechanisms may provoke a greater magnitude and duration of PEH.

Studies have shown lessened peripheral resistance at sites other than the functioning musculature suggesting that there could be a whole body effect (122). It is known that immediately following exercise there is a brief period of hypotension due to a pooling of blood in the vasodilator muscle beds (122). The mechanisms for PEH are dissimilar from this immediate response witnessed post-exercise. Other possible mechanisms could be resetting of baroreceptors, changes in thermoregulation, blood volume, afferent nerve activity, and circulating hormones expressed from an exercise bout. A 2012 paper by Halliwill et al. (70) indicated that much of the PEH can be explained by histaminergic vasodilation, primarily due to the H1 and H2 receptors. Histamine is released in the muscle due to mast cells located in the connective tissue around the muscle degrading and releasing histamine (134). It was shown that blockade of these receptors but not removal of the sympathetic component reduced PEH. Combined H1 and H2 receptor antagonism reduced post-exercise vasodilation by roughly 80% and reduced PEH by 65% (70). It has been suggested that the histamine upregulation associated with PEH may play a role in angiogenesis showcasing other clinical benefits of the PEH response (70).

CHAPTER THREE

METHODOLOGY

Brief Procedures. The study was an experimental design with two phases. Figure 1 gives graphical depiction of the research design. Two groups of subjects were selected via volunteers from e-mail list serves and consisted of obese and normal weight men with PHTN. *Phase 1* consisted of baseline measures and measures following an acute bout of moderate exercise. *Phase 2* consisted of a two-week exercise intervention where all subjects were prescribed the same exercise prescription (65-70% of HR max, 3x/week for 2-weeks) on a cycle ergometer. All exercise sessions were performed in the laboratory under supervision of one of the researchers. Before and after the exercise intervention central and brachial BP, CO, SVR, cfPWV, PWA, and FMD were taken. PEH was assessed following the first exercise session and again following the last (sixth) exercise session. The post-intervention measurements were taken both 24–hours (h) and 48-h after the last exercise session to ensure no acute exercise carry over effect. Subjects were asked to refrain from any addition physical activity over the course of the study.

Subjects. 20 inactive (defined as less than 60 minutes of moderate to vigorous physical activity per week) PHTN (systolic BP (SBP) 120-139 mmHg *or* diastolic BP (DBP) 80-89 mmHg) men were recruited and grouped by body mass index (BMI) and waist circumference into obese (BMI $\geq$ 30 kg/m^2 *and* waist circumference >94 cm) or "lean" (BMI < 25 kg/m^2 *and* waist circumference <94 cm) for this experimental study.

Sample Size Calculation. Sample size was calculated using a 2-sided hypothesis, α= 0.05 and β= 0.20. Previous work using changes in SVR between lean and

obese in response to acute exercise provided the estimates (170). It is estimated that an acute bout of exercise will provoke a 5% SVR mean difference between lean and obese with a standard deviation of 5%. It is estimated that 7 subjects per group will be needed to adequately power the study. Thus, accounting for a 30% drop out, 10 subjects per group (20 total) was needed for this study.

Inclusion Criteria. Obese (BMI $\geq$ 30 kg/m^2 *and* waist circumference $\geq$ 94 cm) and lean (BMI < 25 kg/m^2 *and* waist circumference < 94 cm), inactive (< 60 min of moderate to vigorous physical activity/week, verified by accelerometer), men aged 18-35 yr, and PHTN were included. Waist circumference was used in addition to BMI due to the heterogeneity of the obese phenotype and criticism of prior similar research that only use BMI to determine obesity status (30).

Exclusion Criteria. Those in the "overweight" BMI category (i.e., 25-29.9 kg/m^2) or those with a BMI < 18.5 kg/m^2 or > 40 kg/m^2 were not included in this study. Men over 35 yr old or who registered more than 60 minutes/week of moderate to vigorous physical activity were excluded. Those who answered positively (i.e., yes) on any question of The Physical Activity Readiness Questionnaire (PAR-Q) were excluded from participating in the study. Those with known cardiovascular, pulmonary, renal or metabolic disease, or having symptoms suggestive of these diseases (data were obtained via health history questionnaire) were excluded from the study. Current smokers or anyone with contraindications to vigorous exercise were excluded from the study as well. Subjects on medications used for the treatment of cardiovascular disease were excluded.

Study Design, Visit 1 (Initial Screening Day). See figure 1 for schematic representation of study design. Subjects had their waist circumference, weight and height

measured to determine if their BMI and WC were within the inclusion categories. Those who meet the initial criteria were asked to sit quietly for 5 minutes and then a traditional BP measurement was taken on both left and right arms using an automated BP monitor (Dinamap® PRO 100 Vital Signs Monitor, GE Healthcare) according to the protocol described by the World Health Organization (227). Two additional BP measurements (three total) were taken at 5-minute intervals on both arms. The arm with the highest BP was used to determine baseline BP value. If the average BP from these three measures were within the PHTN range, then subjects were asked to return to the lab for a second screening. In addition, health risk assessment and PAR-Q were used to screen subjects for exclusion criteria previously listed. Subject's physical activity was screened via the Stanford Leisure-Time Activity Categorical Item (L-cat) (104).

To ensure subjects did not change physical activity behavior over the course of the study, participants were asked to wear an activity monitor for seven days prior to the study and over the course of the two-week intervention period. Activity monitors were given to participants after the first visit. Subjects were equipped with a small multisensory activity monitor (Sensewear Pro3 armband) positioned over the right triceps brachii muscle of the right arm at the midpoint between the acromion and the olecranon processes. The activity monitor collects physiological data from the following sensors; a 2 axial accelerometer, a heat flux sensor, a skin temperature sensor, and a galvanic skin response sensor. The monitor uses an onboard algorithm (Inner View TM Professional software 7.0) fitted with anthropometric data from participants (gender, age, height, and weight). Subjects were given activity logs and asked to report wake time, sleep time, and any time the device was removed for longer than 20 minutes. Daytime energy

expenditure, steps, time spent in moderate activity (3-6 METS), and vigorous activity (> 6 METS) were collected for each week.

Visit 2 (2nd BP Screening, Baseline Measures). Three to five days from the first screening visit, subjects returned to the lab for three additional BP measurements (measures will be performed as previously indicated for Visit 1). The total of the six BP measurements (3 from visit 1 and 3 from visit 2) were averaged together to determine if subjects met the PHTN criteria. Subjects were then directed to have a whole body Dual-energy X-ray absorptiometry (DXA) scan to determine body composition. For the DXA assessment, subjects were asked to wear metal-free clothing and to remove any jewelry while lying face up on the DXA scanner bed for approximately 7-10 minutes. DXA was conducted by a certified radiology technician. Following the DXA scan subjects completed a VO_2 peak assessment on an electronically braked cycle ergometer.

VO_2 Max Assessment. All subjects performed a ramp-style maximal exercise test on a cycle ergometer at baseline. Subjects were equipped with a mask attached to a hose connected to a mixing chamber for the metabolic measurement device (Parvo Truemax 2400TM, Parvomedics, Sandy, Utah) to measure ventilation and respiratory gas exchange data and wore a Polar heart rate monitor to measure heart rate (HR) continuously. The Parvo Truemax 2400TM has shown high validity and reliability (10). The metabolic cart was calibrated using the standard three-point calibration before each test. After collecting resting data for 2 minutes, subjects performed a 5-minute warm-up at 50 Watts on the cycle ergometer, pedaling at a cadence of their choice (subjects were encouraged to maintain this cadence for the remainder of the test). After the warm-up phase, load was increased by 30 watts every minute until the subject could not continue. Verbal

encouragement was given to all subjects throughout the entire test. The average of the two highest consecutive 15-second oxygen uptake averages during the test was taken as the peak VO_2.

Visit 3 (<u>Phase 1</u> Acute Exercise Response). Previous research has established that the greatest PEH response occurs in the afternoon hours compared to the morning hours (92). To control for potential diurnal effects and maximize the PEH response, visit three was performed at the same time of day (± 30 minutes) in the afternoon (approximately 1 pm). Participants were fasted for at least 5 h, asked to refrain from caffeine and alcohol for 24 h and asked to refrain from unaccustomed physical activity for 48 h prior to their visit to avoid potential carry over effects from previous activity. Subjects were instructed to avoid antihistamines for 5 days prior to each visit to avoid the actions of these agents on the vasculature (125). Oral vitamin C supplementation was restricted for 3 days prior to the study. Subjects were asked to eat their breakfast no later than 8 am the morning of this visit and the morning of the post intervention measurement. Subjects were asked to consume the same dinner and amount of fluids the night before visit three and the post-intervention measurements and the same breakfast and fluids the morning of visit 3 and the post-intervention measurements. Subjects were asked to record their meals to ensure compliance with this requirement. Liquids were tracked via instruction to the subjects to drink from a bottle with a known quantity, and to maintain that quantity between visit three and the post-intervention measurements.

Acute Exercise Assessments. Upon arrival at the research facility subjects were directed to lie supine for 20 minutes to achieve hemodynamic stability. Baseline measurements of cfPWV, PWA, central and brachial BP, CO and SVR (measured non-

invasively via the PhysioFlow) were then assessed. Following baseline measures, subjects performed a 40-minute exercise bout on a cycle ergometer at a HR that elicited 65-70% of their measured VO_2peak. To warm up, subjects began cycling at a light work rate of approximately 25 watts for 5 minutes. Wattage then increased to elicit the desired HR. Work rate was adjusted if needed to keep HR within ± 5 beats of this value. Subjects were given a 5-minute cool-down period at approximately 25 Watts. Following exercise, subjects remained in the laboratory for an additional hour in a supine position. Central BP, brachial BP, and PWA was measured every 5 minutes following exercise for one hour (12 total measures). cfPWV was measured twice following exercise, 30 minutes and then 60 minutes following exercise. The PhysioFlow remained connected to the subjects throughout the entire visit and data was collected in 10-second averages. The time frame of measurement was chosen due to previous research illustrating the greatest hypotensive response to acute exercise is within the first hour (190).

Visits 4-8 (Phase 2: Aerobic Training): Subjects returned to the laboratory for a total of 6 exercise days (i.e., visit 3 plus 5 additional days) over two weeks. All training was completed at the laboratory under direct supervision of one of the investigators. Subjects were equipped with a HR monitor and then asked to perform a 40-minute exercise bout on a cycle ergometer at a HR that elicits 65-70% of their measured VO_2peak. To ensure exercise prescription adherence, subjects were provided verbal and visual HR feedback and encouraged to maintain this value for the entire exercise bout. To warm up, subjects began cycling at a light work rate of approximately 25 watts for 5 minutes. Work rate was adjusted if needed to keep HR within ± 5 beats of this value. Subjects were given a 5-minute cool-down period at approximately 25 watts.

Following *visit 8* (6th and last training session) post-exercise hemodynamic response to exercise was assessed once again. Subjects were asked to remain in the laboratory for an additional hour in a supine position while the same measurement protocol as described above was followed.

Visit 9 and 10 (Assessment of Aerobic Training Response): At 24 and 48 h following the last exercise session, subjects were asked to return to the laboratory for final cardiovascular measurements. Upon arrival subjects were directed to lie supine for 20 minutes to achieve hemodynamic stability. Measurements of cfPWV, PWA, central and brachial BP, CO and SVR were taken as previously described.

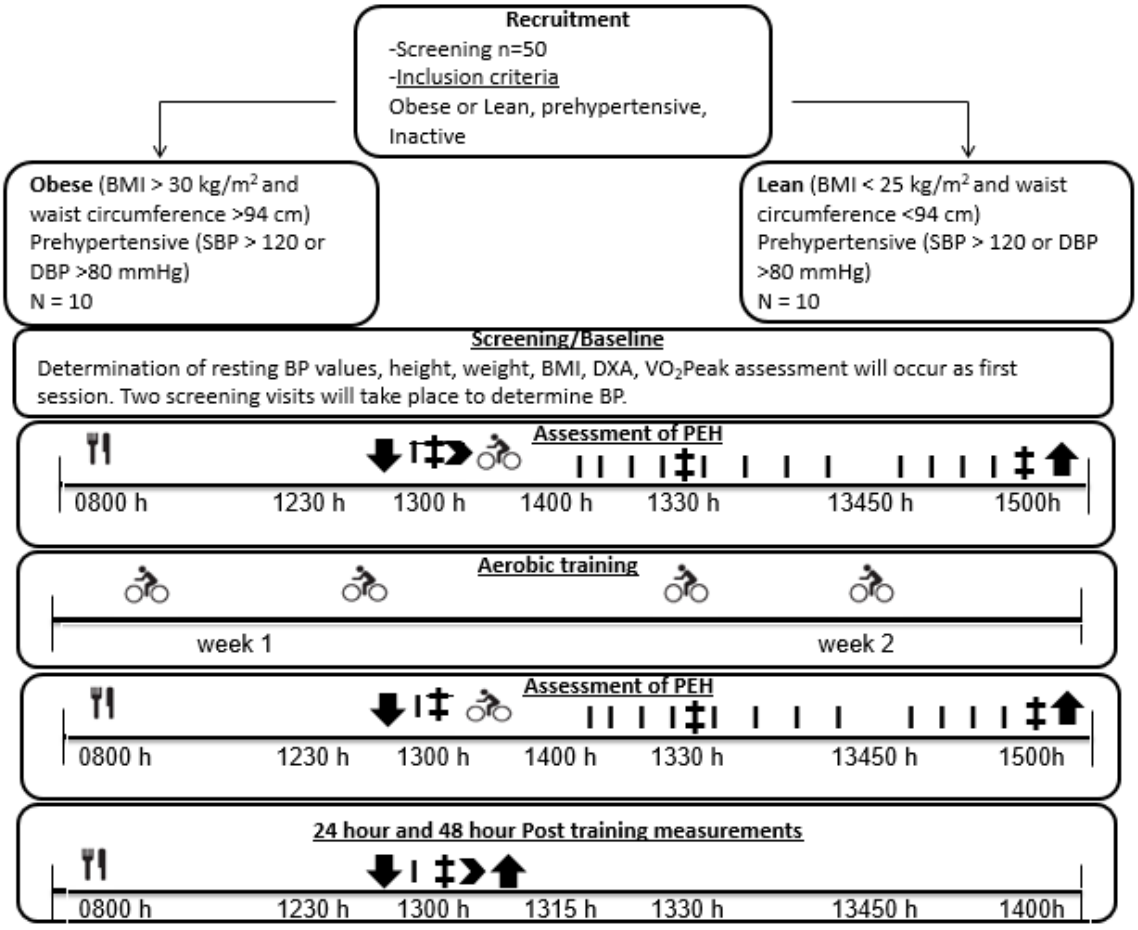


Figure 1. Schematic overview of the experimental period. Subjects will be asked to finish breakfast by 0800 h ( ). Body fat, BP and VO_2peak will be measured prior to the PEH assessment visit. During the PEH visits, cardiovascular assessments of central/brachial BP, PWA, and cfPWV will be measured prior to exercise on the first and last exercise session and following exercise for one hour. CO and TPR will be measured continuously from approximately 1240 h ( ) to 1400 h( ). 40 minutes of cycling ( ) will be performed at an intensity of 65-70% HR max. Every 5 minutes following exercise, subjects will have central/peripheral BP and PWA assessments ( ). 30 minutes and 60 minutes following exercise subjects will have cfPWV assessed ( ). FMD will be measured at baseline and then at 24 and 48 hours following the last training session ( ). Subjects will engage in 6 total training sessions followed by post-intervention assessments at 24 and 48 hours following the last exercise session.

Measurements. CO and SVR were measured continuously at visit three and the post-intervention measurement via the PhysioFlow device (Manatec Biomedical, Paris, France). The PhysioFlow has been found valid and reliable at rest and during low- to maximal-intensity exercise in normal weight, and overweight individuals (26, 167). The PhysioFlow uses changes in transthoracic impedance during cardiac ejection to calculate

SV, which is multiplied by HR to provide an estimate of CO. Sensors on the neck, chest, and back are used to transmit and detect electrical and impedance changes in the thorax (see figure 2). This is used to measure and calculate hemodynamic parameters. The following procedures have been detailed prior (26) but summarized below. Subjects were directed to lie supine in a quiet, temperature-controlled room, and prepped to have two sets of two electrodes placed on the body. One "transmitting" electrode and one "sensing" electrode was be placed above the supraclavicular fossa at the left base of the neck and along the xiphoid process, respectively. Another set of two electrodes are used to monitor a single ECG lead (V1/V6 position). SBP/DBP were measured automatically via the SphygmoCor device from the brachial artery at rest and every 5 minutes following exercise and transferred into the impedance cardiograph device, which calculates mean arterial pressure to estimate SVR.

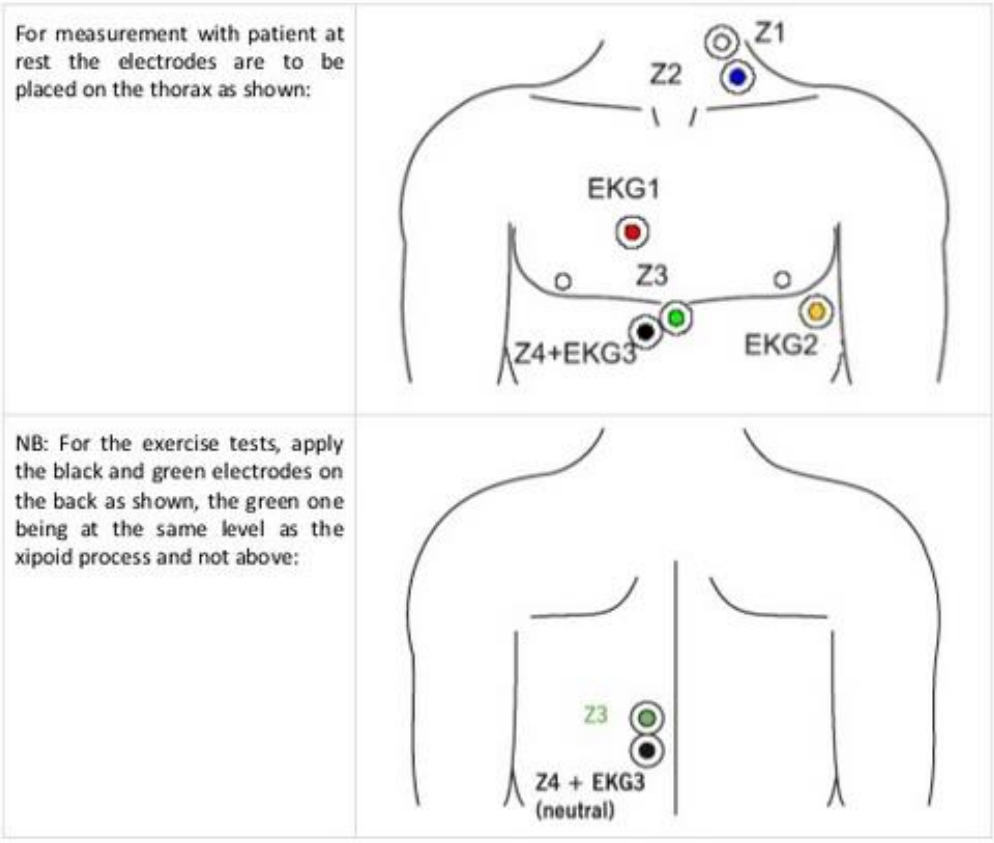


Figure 2. Pictorial representation of electrode placement of PhysioFlow device

Pulse wave velocity (PWV)/pulse wave analysis (PWA). Central/brachial BP, cfPWV, and PWA measurements were taken using the SphygmoCor XCEL™ (AtCor Medical, Sydney, NSW, Australia) by means of validated methodology (206). The SphygmoCor MM3 (ArCor Medical) is a well-validated (1, 154) and extensively used system. The newer XCEL™ device has also been shown valid and reliable (84) and uses a simpler, more convenient approach to measure arterial stiffness and wave reflection characteristics. All measurements were taken in the supine position in a quiet, temperature-controlled room after 20 minutes of rest and 2 sequential arterial BP measurements that confirm hemodynamic stability.

PWA was performed by deriving an ascending aortic pressure waveform from the brachial artery waveforms recorded at the arm, using a specialized cuff containing a high-fidelity micromanometer. After 10 sequential, high-quality waveforms (software derived from an algorithm including average pulse height, pulse height variation, diastolic variation, and the maximum rate of rise of the peripheral waveform) are acquired, a validated generalized transfer function is used to generate the corresponding central aortic pressure waveform. The Aix is calculated as the difference between the first and second systolic peaks of the ascending aortic waveform expressed as a percentage of the central pulse pressure (the difference between central systolic and diastolic pressure). Because Aix is influenced by HR, an index normalized for a HR of 75 beats/minute (Aix at HR75) will be used.

Carotid-femoral pulse wave velocity (cfPWV) was determined by simultaneously recording carotid artery wave forms by applanation tonometry and femoral artery waveforms using a specialized micromanometer equipped cuff. Distances from the carotid sampling site to the suprasternal notch and from the suprasternal notch to the femoral cuff was measured as straight lines between the points on the body surface using a tape measure. The distance from the femoral arterial pulse to the femoral cuff was obtained and subtracted from the total distance (D). The time (t) between the onset of femoral and carotid waveforms is determined as the mean from 10 consecutive cardiac cycles. The cfPWV is calculated from the distance between measurement points and the time delay (t) as follows: PWV = D/t (m/sec), where D is distance in meters and t is the time interval in seconds.

Statistical Analysis. Data was analyzed using SPSS software (version 20). Data are expressed as ± standard deviation (SD). All *P* values were calculated assuming two-tailed hypothesis; $P < 0.05$ is considered statistically significant. Data were analyzed for normality and transformed if necessary. Descriptive statistics were used for the demographics of the subjects. The physical activity data, BP (brachial and central), arterial stiffness indices, and hemodynamic outcomes between the 2 groups (lean and obese) by 2 conditions (control and exercise) over the hour measurement period following exercise and pre post BP values will be assessed via Linear Mixed Models. The analysis will be conducted in a hierarchical fashion using Restricted Maximum Likelihood model and 'variance components' covariance error structure. PEH used to predict chronic training BP changes will be calculated as the difference between pre-exercise resting BP and the lowest 5-minute rolling average BP in the post-exercise period. Pearson correlation will be used to assess the relationship between the magnitude of PEH from the first exercise session and the final resting BP value following aerobic training.

CHAPTER FOUR

RESULTS

Baseline Characteristics. Twenty subjects (10 obese, 10 lean) started the intervention, four subjects, two from each group, dropped out for unrelated reasons resulting in 16 subjects, eight per group, completed the study. Table 1 outlines the subject's physical activity characteristics by group over the course of the two-week intervention and one week of baseline. For daytime energy expenditure and steps, there was no group difference ($P = 0.301$, $P = 0.936$, respectively), week differences ($P = 0.978$, $P = 0.581$, respectively), or group by week interaction ($P = 0.807$, $P = 0.180$, respectively). There were significant group differences for minutes of moderate activity and vigorous activity per week between groups ($P = 0.23$, $P = 0.001$, respectively). There was however no significant difference in time spent in moderate or vigorous activity over the course of the intervention and baseline period ($P = 0.390$, $P = 0.587$, respectively) and there was no significant group by week interaction ($P = 0.757$, $P = 0.190$, respectively). Table 2 details baseline demographic information by group. There were no significant baseline differences for brachial SBP (BSBP) or DBP (BDBP), age, or VO_2 peak (all $P > 0.05$). There were however, significant differences between groups for BMI, waist circumference, total body fat, and visceral fat (all $P < 0.05$).

Table 1. Physical activity characteristics by group over the course of the intervention and baseline period.

	Baseline	week 1	week 2
Energy expenditure (Kcal/day)			
Lean	2490 ± 631	2524 ± 511	2485 ± 465
Obese	2709 ± 404	2655 ± 412	2712 ± 475
Steps			
Lean	6517 ± 3823	6078 ± 3251	6585 ± 4025
Obese	6239 ± 2853	6465 ± 2547	5473 ± 2669
Moderate activity (min/day)			
Lean	66 ± 33	74 ± 29	67 ± 29
Obese	52 ± 24[α]	53 ± 21[α]	43 ± 23[α]
Vigorous activity (min/day)			
Lean	4 ± 4	3 ± 3	2 ± 3
Obese	.5 ± 1[α]	1 ± .2[α]	1 ± 2

[α]Represents significant group difference ($P < 0.05$)

Table 2. Demographic mean values ± SD (range) for subjects at rest by group.

	Lean (n = 8)	Obese (n = 8)	P-value
Brachial SBP (mm Hg)	126 ± 7 (22)	126 ± 5 (10)	0.976
Brachial DBP (mm Hg)	76 ± 4 (15)	77 ± 7 (11)	0.567
Age (yr)	24 ± 4 (19)	25 ± 4 (10)	0.547
VO_2peak ($l.min^{-1}$)	2.9 ± .4 (1.4)	3.2 ± .7 (2.0)	0.248
BMI (kg/m^2)	23 ± 2 (5)	34 ± 3 (8)	< 0.001
Weight (kg)	72 ± 19 (21)	104 ± 20 (64)	< 0.001
Waist (cm)	81 ± 3 (9)	133 ± 40 (102)	0.002
Body fat (%)	23 ± 7 (17)	35 ± 2 (5)	< 0.001
Visceral fat (cm^3)	279 ± 224 (605)	1471 ± 374 (1060)	< 0.001

Table 3 further outlines baseline resting hemodynamic characteristics between groups. There were no baseline resting HR or central BP differences between groups (all $P > 0.05$). Overall, obese PHTN was characterized by increased central arterial stiffness as witnessed by significant differences between groups for Ap ($P < 0.001$) and Aix @ HR 75 ($P = 0.002$). There was no PWV difference between groups. As was hypothesized, the obese phenotype was characterized by a significantly higher CO ($P = 0.005$) and SV ($P = 0.013$) while the lean phenotype showed significantly higher SVR ($P = 0.003$). There were no resting group differences on cardiac index ($l/min/m^2$), stroke volume index (ml/m^2), and systemic vascular resistance index ($Dyn.s/cm5.m^2$). This suggests the differences seen between groups are due to body mass.

Table 3. Baseline hemodynamic characteristics by group.

	Lean (n = 8)	Obese (n = 8)	P-value
Central SBP (mm Hg)	110 ± 5	113 ± 6	0.123
Central DBP (mm Hg)	77 ± 4	79 ± 7	0.316
Ap (mm Hg)	.63 ± 2	4.5 ± 4	0.001
Aix @ HR 75 (%)	-2.1 ± 7	6.1 ± 12	0.02
PWV (m/s)	6.0 ± .7	6.6 ± .8	0.237
HR (bpm)	64 ± 10	66 ± 7	0.729
CO (l/min)	4.7 ± 1	6.3 ± 1	0.005
Ci ($l/min/m^2$)	2.5 ± .4	2.7 ± .6	0.387
SV (ml)	75 ± 15	101 ± 21	0.013
Svi (ml/m^2)	40 ± 7	42 ± 8	0.6
SVR ($Dyn.s/cm^5$)	1604 ± 444	1218 ± 263	0.003
SVRi ($Dyn.s/cm5.m^2$)	2956 ± 867	2783 ± 547	0.429

Ci (cardiac index), Svi (Stroke volume index),
SVRi (Systemic vascular resistance index)

Table 3. Acute exercise response between group before intervention (untrained) and following five exercise sessions (trained).

	Untrained baseline rest	Untrained acute exercise response	Trained baseline rest	Trained acute exercise response
BSBP (mm Hg)				
Lean	127 ± 7	124 ± 7*	120 ± 13*	124 ± 8$^{\beta}$
Obese	126 ± 5	130 ± 8$^{\alpha\alpha}$	125 ± 11	127 ± 7
BDBP (mm Hg)				
Lean	76 ± 8	75 ± 6	73 ± 10*	74 ± 7
Obese	77 ± 11	76 ± 7	76 ± 12	75 ± 7
CSBP (mm Hg)				
Lean	110 ± 7	107 ± 5*	105 ± 12*	107 ± 8$^{\beta}$
Obese	113 ± 6	116 ± 8$^{\alpha\alpha}$	112 ± 11$^{\alpha}$	112 ± 7
CDBP (mm Hg)				
Lean	77 ± 4	77 ± 6	74 ± 11	75 ± 7
Obese	79 ± 7	78 ± 7	77 ± 11	75 ± 7
Ap (mm Hg)				
Lean	1 ± 2	-.8 ± 4*	1 ± 7	.6 ± 4
Obese	5 ± 6$^{\alpha}$	6 ± 5$^{\alpha\alpha}$	5 ± 8$^{\alpha}$	6 ± 5
AIx (%)				
Lean	-2.4 ± 7	-2.2 ± 7	2 ± 12*	2 ± 8

Obese	6 ± 12$^{\alpha}$	12 ± 8$^{\alpha\alpha}$*	9 ± 13	13 ± 8
PWV (m/s)				
Lean	6.0 ± .7	5.8 ± .7	6.1 ± .8	6.1 ± .8
Obese	6.5 ± .9	6.5 ± .8	6.6 ± .8	6.7 ± .7
HR (bpm)				
Lean	64 ± 10	75 ± 11*	62 ± 11*	70±13**$^{\beta}$
Obese	64 ± 7	72 ± 9*$^{\alpha\alpha}$	67 ± 10$^{\alpha}$	72±10**$^{\alpha\alpha}$
SV (ml)				
Lean	74 ± 13	74 ± 14	82 ± 16*	83 ± 19
Obese	106 ± 21$^{\alpha}$	102 ± 24*$^{\alpha\alpha}$	99 ± 20*	94 ± 18**$^{\alpha\alpha}$
CO (L/min)				
Lean	4.5 ± 1	5.4 ± 1*	5.0 ± 1*	5.7 ± 1**
Obese	6.7 ± 1$^{\alpha}$	7.2 ± 2*$^{\alpha\alpha}$	6.5 ± 1*$^{\alpha}$	6.7± 1**$^{\alpha\alpha\beta}$
SVR (Dyn.s/cm5)				
Lean	1605 ± 444	1381 ± 300*	1465 ± 299*	1361±533**$^{\beta}$
Obese	1141 ± 263$^{\alpha}$	1066 ± 256*$^{\alpha\alpha}$	1119 ± 339$^{\alpha}$	1110±341$^{\alpha\alpha\beta}$

*Significant difference from pre-trained baseline

**Significant difference from trained baseline

$^{\alpha}$Significant between group differences

$^{\alpha\alpha}$Significant between group over time interactions

$^{\beta}$Significant within group pre-trained, trained over time interactions (all $P < 0.05$)

Table 4. Acute exercise response between group before intervention (untrained) and following five exercise sessions (trained).

	Untrained baseline rest	Untrained acute exercise response	Trained baseline rest	Trained acute exercise response
BSBP (mm Hg)				
Lean	127 ± 7	124 ± 7*	120 ± 13*	124 ± 8$^{\beta}$
Obese	126 ± 5	130 ± 8$^{\alpha\alpha}$	125 ± 11	127 ± 7
BDBP (mm Hg)				
Lean	76 ± 8	75 ± 6	73 ± 10*	74 ± 7
Obese	77 ± 11	76 ± 7	76 ± 12	75 ± 7
CSBP (mm Hg)				
Lean	110 ± 7	107 ± 5*	105 ± 12*	107 ± 8$^{\beta}$
Obese	113 ± 6	116 ± 8$^{\alpha\alpha}$	112 ± 11$^{\alpha}$	112 ± 7
CDBP (mm Hg)				
Lean	77 ± 4	77 ± 6	74 ± 11	75 ± 7
Obese	79 ± 7	78 ± 7	77 ± 11	75 ± 7
Ap (mm Hg)				
Lean	1 ± 2	-.8 ± 4*	1 ± 7	.6 ± 4
Obese	5 ± 6$^{\alpha}$	6 ± 5$^{\alpha\alpha}$	5 ± 8$^{\alpha}$	6 ± 5

AIx (%)				
Lean	-2.4 ± 7	-2.2 ± 7	2 ± 12*	2 ± 8
Obese	6 ± 12$^{\alpha}$	12 ± 8$^{\alpha\alpha}$*	9 ± 13	13 ± 8
PWV (m/s)				
Lean	6.0 ± .7	5.8 ± .7	6.1 ± .8	6.1 ± .8
Obese	6.5 ± .9	6.5 ± .8	6.6 ± .8	6.7 ± .7
HR (bpm)				
Lean	64 ± 10	75 ± 11*	62 ± 11*	70 ± 13**$^{\beta}$
Obese	64 ± 7	72 ± 9*$^{\alpha\alpha}$	67 ± 10$^{\alpha}$	72 ± 10**$^{\alpha\alpha}$
SV (ml)				
Lean	74 ± 13	74 ± 14	82 ± 16*	83 ± 19
Obese	106 ± 21$^{\alpha}$	102 ± 24*$^{\alpha\alpha}$	99 ± 20*	94 ± 18**$^{\alpha\alpha}$
CO (L/min)				
Lean	4.5 ± 1	5.4 ± 1*	5.0 ± 1*	5.7 ± 1**
Obese	6.7 ± 1$^{\alpha}$	7.2 ± 2*$^{\alpha\alpha}$	6.5 ± 1*$^{\alpha}$	6.7 ± 1**$^{\alpha\alpha\beta}$
SVR (Dyn.s/cm^5)				
Lean	1605 ± 444	1381 ± 300*	1465±299*	1361.5±533**$^{\beta}$
Obese	1141 ± 263$^{\alpha}$	1066 ± 256*$^{\alpha\alpha}$	1119±339$^{\alpha}$	1110 ± 341$^{\alpha\alpha\beta}$

**Significant difference from trained baseline

$^{\alpha}$Significant between group differences

$^{\alpha\alpha}$Significant between group over time interactions

$^{\beta}$Significant within group pre-trained, trained over time interactions (all $P < 0.05$)

Acute Exercise Response. Figure 3 illustrates that lean PHTN had a significant BSBP reduction averaging 3 ± 9 mm Hg ($P = 0.014$) following acute exercise while obese PHTN had a 3 mm Hg increase following an acute bout of exercise ($P = 0.022$). There was a significant 5 ± 8 mm Hg BSBP group difference over the course of the hour following exercise ($P < 0.001$). There was also a significant BSBP group by time interaction ($P = 0.021$). There was no significant BDBP or CDBP PEH, group over time change, or time by group interactions for either group (all $P > 0.05$). Figure 4 shows that lean PHTN CSBP had a significant PEH effect, averaging a 3 ± 8 mm Hg reduction compared to pre-exercise values ($P < 0.001$) while obese PHTN had a 3 mm Hg CSBP increase ($P = 0.018$). There was a significant group over time difference ($P < 0.001$) for CSBP with lean PHTN averaging 8 ± 8 mm Hg lower than obese PHTN. There was also a significant group by time interaction for CSBP ($P = 0.002$).

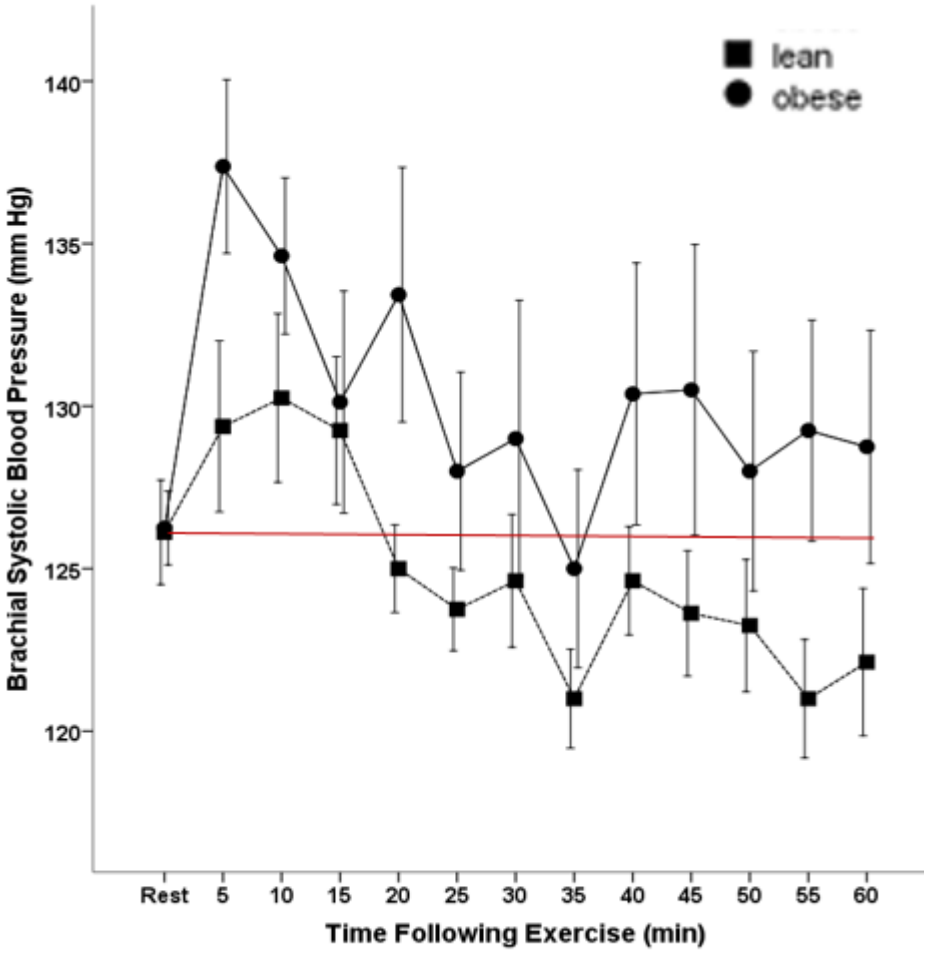


Figure 3. Mean BSBP at rest and for 60 min following exercise for lean PHTN and obese PHTN. Error bar +/- 1 SE

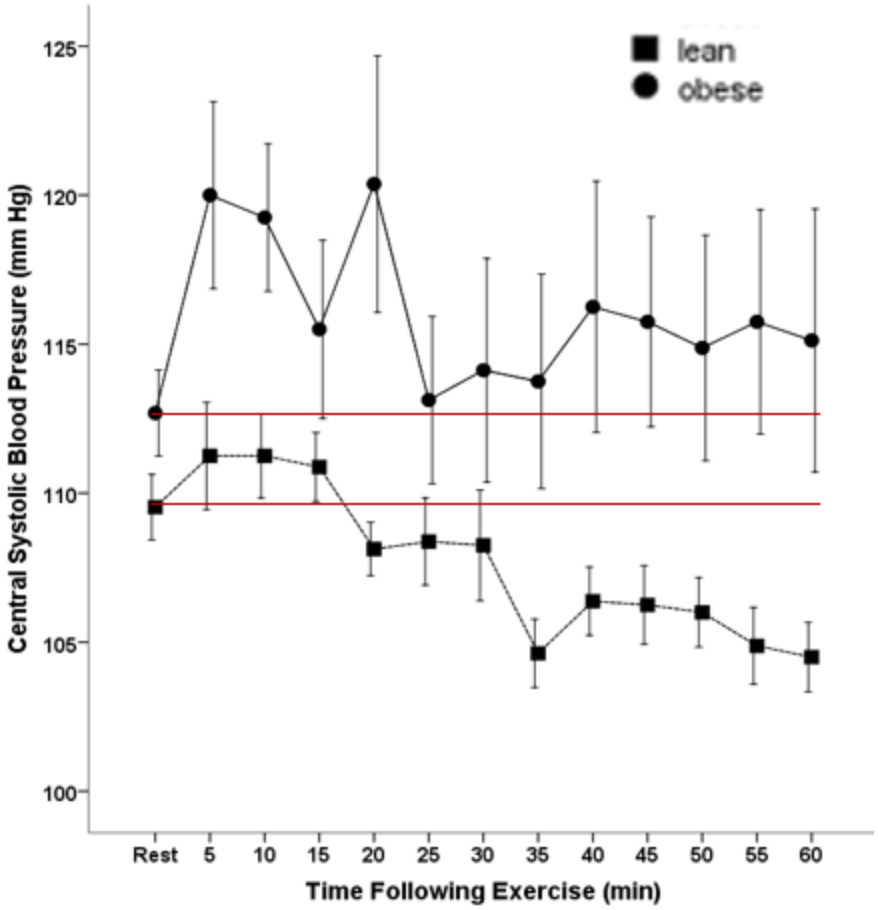


Figure 4. Mean CSBP at rest and for 60 min following exercise for lean PHTN and obese PHTN. Error bar +/- 1 SE

Figure 5 shows a significant Ap reduction of 1.9 ± 5 mm Hg during the post exercise period for lean PHTN (P = 0.024) with a borderline significant increase in obese PHTN (P = 0.055). There was also a significant mean group difference of 6 ± 5 mm Hg and a significant group by time interaction (P = 0.021). Figure 6 shows a significant Aix @ HR 75 group difference of 14 ± 8% (P < 0.001) following exercise with a significant group by time interaction (P = 0.021). There was no within group difference when comparing pre-exercise rest to post -exercise rest on Aix @ HR 75 for lean PHTN (P = 0.672). Obese PHTN showed a significant within group increase of approximately 6 ±

8% Aix @ HR 75 (P = 0.013). There was a significant group by time interaction (P = 0.004). There was no significant post exercise PWV (m/s) change in lean PHTN (P = 0.511) or obese PHTN (P = 0.945). There was however a -.7 ± .7 m/s significant group difference over the course of the recovery period (P = 0.017). There was no acute exercise group by time interaction for PWV (P = 0.835). There were significant baseline differences, within group over time differences, and group by time interactions for SV (figure 7), CO (figure 8), and SVR (figure 9) between groups (all P < 0.001). Figure 10 shows that there were no HR group differences at rest (P = 0.467), during exercise (P = 0.082) or during the recovery period (P = 0.483). However, there was significant within group over time HR differences in both groups (P < 0.001) and a significant group by time interactions for HR (P = 0.023).

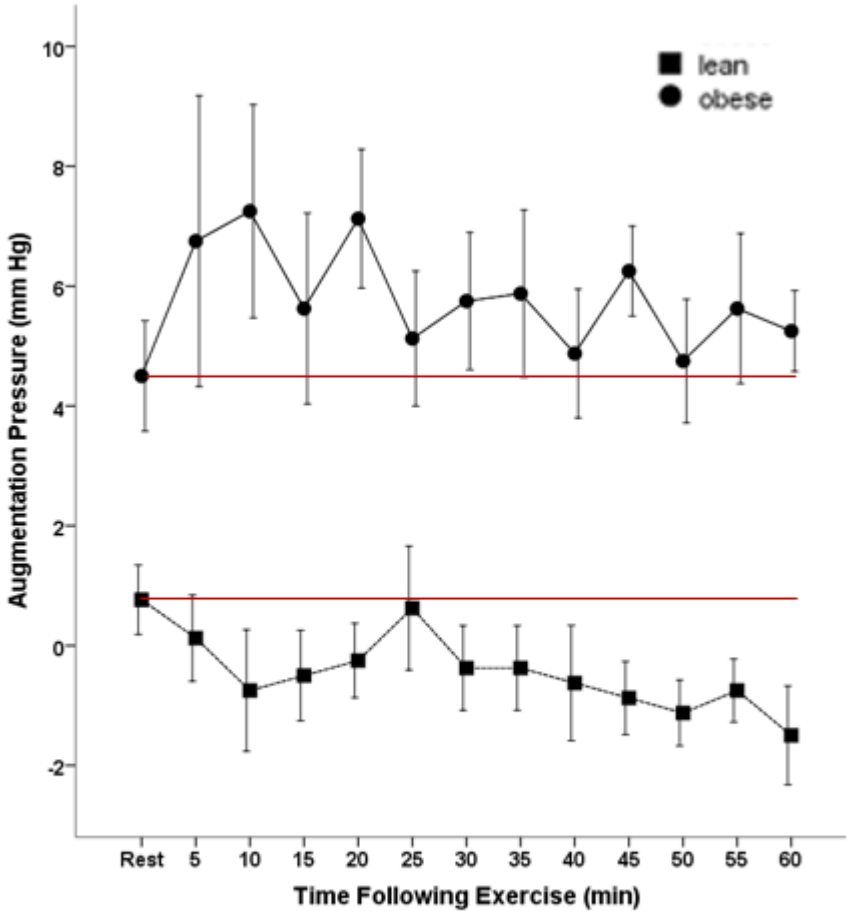


Figure 5. Mean Ap at rest and for 60 min following exercise for lean PHTN and obese PHTN. Error bar +/- 1 SE

Table 5. Mean (± SD) resting values at baseline, 24 h and 48 h following the last training session between group.

	Baseline	24 h following	48 h following
Brachial SBP (mm Hg)			
Lean	126 ± 7	122 ± 6*	122 ± 6*
Obese	126 ± 5	127 ± 6	127 ± 4[a]
Brachial DBP (mm Hg)			
Lean	76 ± 4	76 ± 6	76 ± 6
Obese	78 ± 7	74 ± 7	75 ± 8
Central SBP (mm Hg)			
Lean	110 ± 5	108 ± 5	107 ± 5*
Obese	113 ± 6	112 ± 6[a]	113 ± 6[a]
Central DBP (mm Hg)			
Lean	77 ± 4	77 ± 4	77 ± 4
Obese	80 ± 7	75 ± 7*	76 ± 7
AP (mm Hg)			
Lean	.63 ± 2	.45 ± 2	.12 ± 2
Obese	4.5 ± 4[a]	4.9 ± 3[a]	4.3 ± 3[a]
Aix (%)			
Lean	-2.1 ± 7	-4.9 ± 7	-5.0 ± 7
Obese	6.1 ± 12[a]	7.4 ± 9[a]	6.1 ± 11[a]

PWV (m/s)			
Lean	6.0 ± .7	6.1 ± .9	6.0 ± .7
Obese	6.6 ± .8	6.6 ± .8	6.7 ± .8
SV (ml)			
Lean	75.1 ± 15	80.5 ± 13*	81.2 ± 14*
Obese	100.8 ± 21[α]	89.2 ± 19*[α]	92.2 ± 21**[α]
HR (bpm)			
Lean	64 ± 10	63 ± 11	63 ± 10*
Obese	66 ± 7	66 ± 9	64 ± 7*
CO (L/min)			
Lean	4.7 ± 1	5.0 ± 1*	5.0 ± 1*
Obese	6.3 ± 1[α]	5.8 ± 1*[α]	5.8 ± 1*[α]
SVR (Dyn.s/cm^5)			
Lean	1604.3 ± 444	1435.5 ± 267*	1467.6 ± 296*
Obese	1218.2 ± 263[α]	1265.3 ± 270*[α]	1313.3±303**[α]

*Significant difference from pre-trained baseline
**Significant difference from 24 h following
[α]Significant between group differences (all $P < 0.05$)

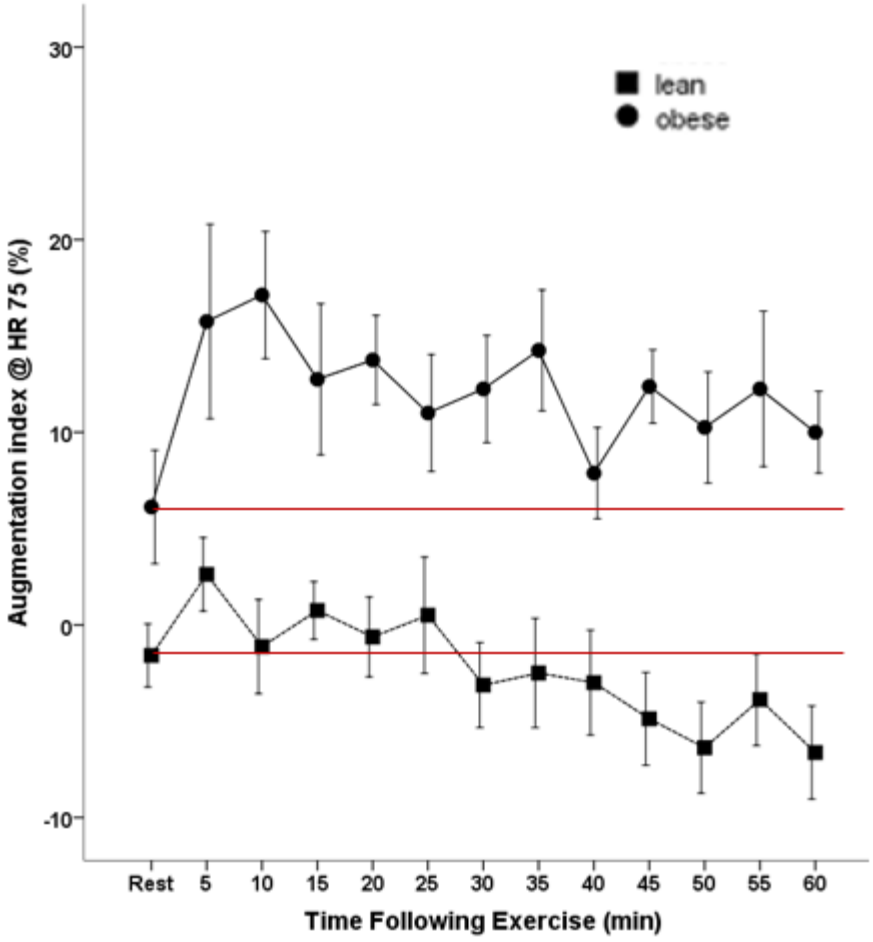


Figure 6. Mean Aix @ HR 75 at rest and for 60 min following exercise for lean PHTN and obese PHTN. Error bar +/- 1 SE

Training adaptations. Table 4 details the pre-trained acute and trained acute hemodynamic response for both groups. Following exercise training, lean PHTN showed a significant increase in BSBP in response to acute exercise (P = 0.018) with no acute exercise response for obese PHTN (P = 0.152). Trained baseline BSBP was significantly reduced from untrained baseline BSBP for the lean PHTN group (P = 0.022). Figure 10 shows lean PHTN BSBP response to acute exercise at a pre-trained state and a trained state. If baseline BSBP is removed there is no significant lean PHTN BSBP difference between untrained and trained response (125 ± 6 mm Hg compared to 126 ± 9 mm Hg, P

= 0.584). There was a significant training interaction from moving from untrained to trained for lean PHTN (P = 0.033). There was a borderline significant within group pre-trained to trained interaction for lean PHTN when examining CSBP (P = 0.058). Both groups witnessed a significant HR and SVR pre-trained to trained interaction in response to acute exercise (P < 0.001). The obese group experienced a significant SV and CO pre-trained to trained interaction in response to acute exercise (both P < 0.001).

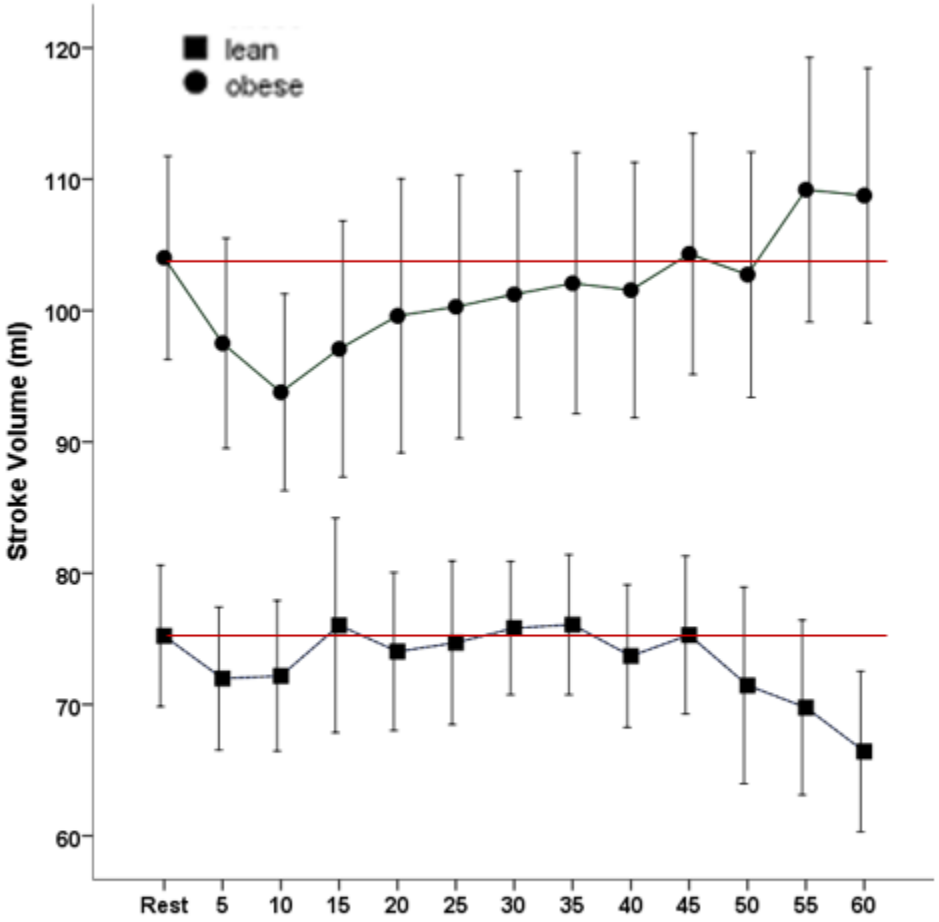


Figure 7. Mean SV (ml) at rest and 60 min following exercise for lean PHTN and obese PHTN. Data averaged every 5 minutes. Error bar +/- 1 SE.

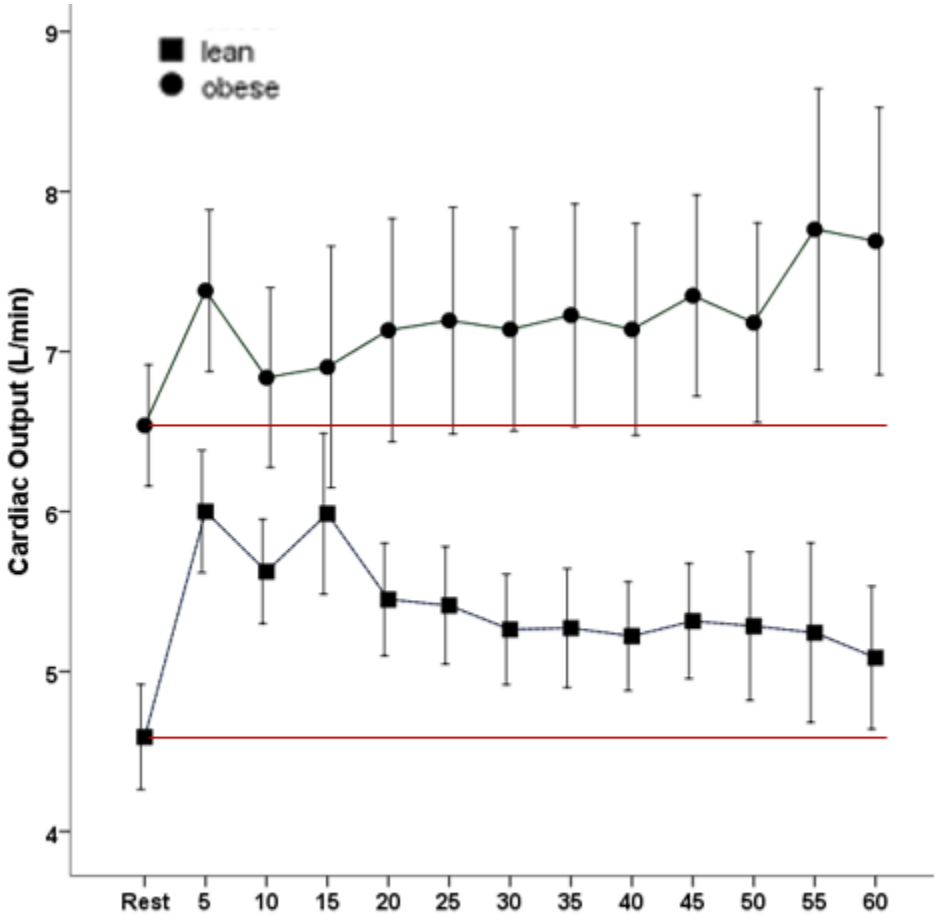


Figure 8. Mean CO (L/min) at rest and 60 min following exercise for lean PHTN and obese PHTN. Data averaged every 5 minutes. Error bar +/- 1 SE.

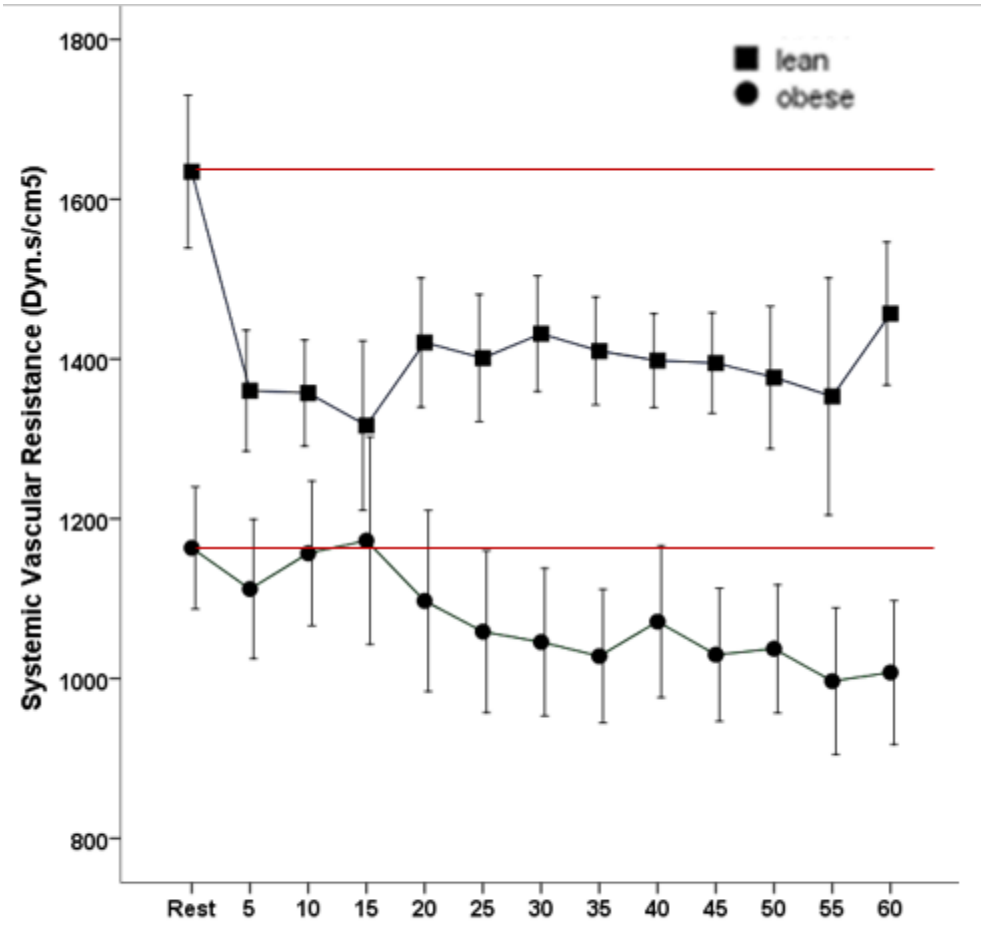


Figure 9. Mean SVR at rest and 60 min following exercise for lean PHTN and obese PHTN. Data averaged every 5 minutes. Error bar +/- 1 SE.

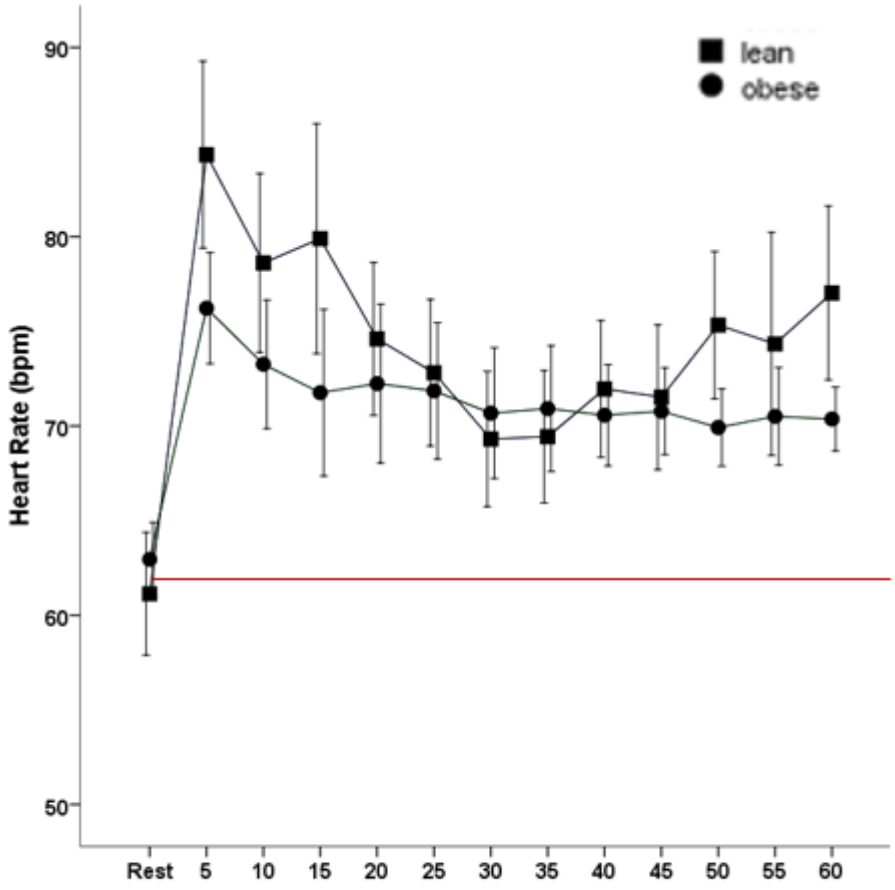


Figure 10. Mean HR (bpm) at rest and following exercise for lean PHTN and obese PHTN. Data averaged every 5 minutes. Error bar +/- 1 SE.

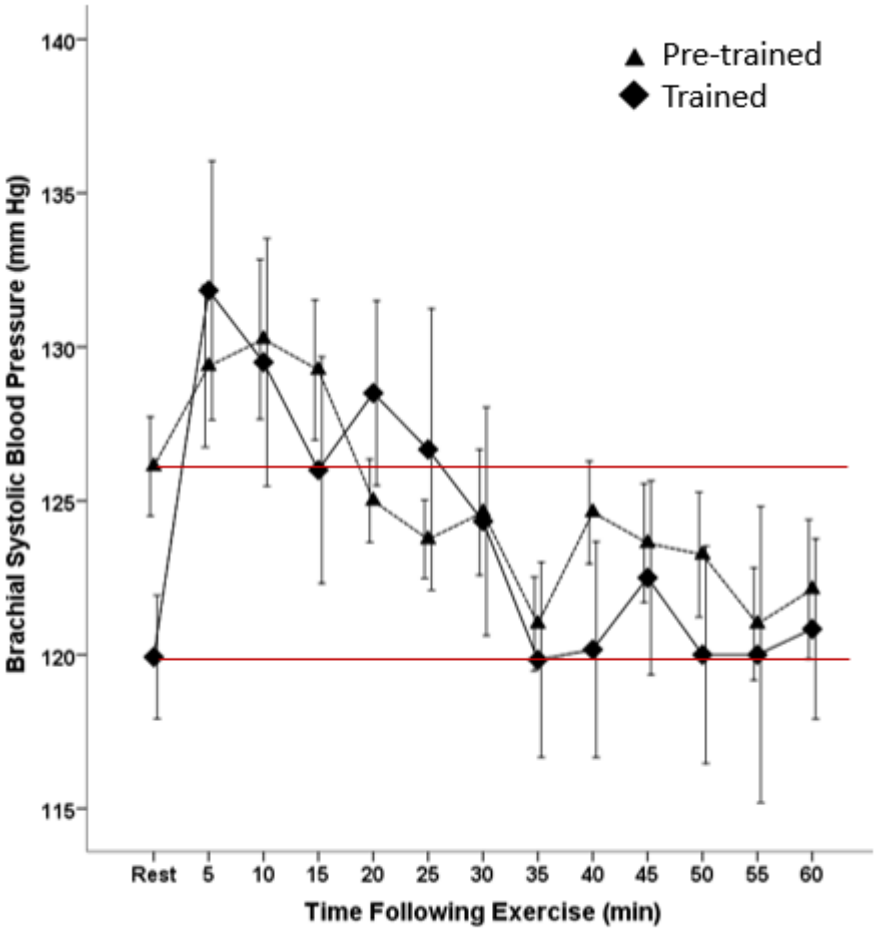


Figure 11. Pre-trained and trained BSBP rest and for 60 min following exercise for lean PHTN. Error bar +/- 1 SE

Table 5 shows both within group and between group training effects. Figure 11 illustrates that lean PHTN witnessed a significant 4 mm Hg decrease in BSBP between baseline and 24 h post (P = 0.022) and a 3 mm Hg decrease between baseline and 48 h post (P = 0.039). There were no significant changes for obese PHTN on BSBP (P = 0.225). There was a significant group by time interaction for BSBP (P = 0.020) insomuch that following training there were significant group differences in resting BSBP and CSBP. The only DBP (central and brachial) training affect seen in either group was obese PHTN CDBP and this occurred 24 h following the last exercise session. Figure 12 shows a decrease with lean PHTN in CSBP between baseline and following

five training sessions (P = 0.007) and 48 h following the last exercise session (P = 0.049). There was no significant training effect in either group for Ap (P = 0.514), Aix (P = 0.096), or PWV (P = 0.982). Both SV and CO (Figure 13) were significantly increased at 24 h and 48 h post training for lean PHTN (P < 0.001). Within obese PHTN, SV and CO were significantly decreased at both 24 h and 48 h following the last training session (P < 0.001). HR significantly decreased by approximately 1 bpm only between baseline and 48 h post last training session for both groups (P < 0.001). SVR significantly decreased from baseline to 24 h and 48 h following the last session for lean PHTN while significantly increasing at 24 h and 48 h following the last training session for obese PHTN (both P < 0.001).

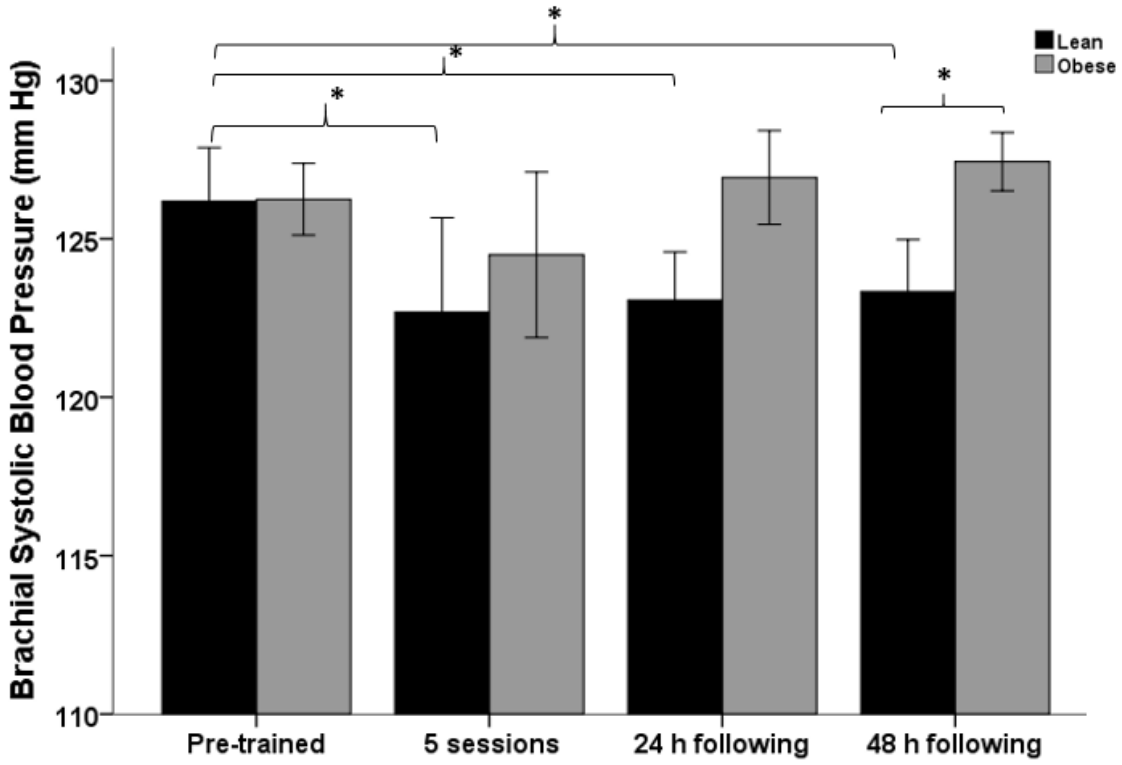


Figure 12. Resting pre-trained, before the 6th exercise session, 24 and 48 h following the 6th exercise session for lean PHTN and obese PHTN. *Represents significantly different from baseline (P < 0.05). Error bar +/- 1 SE

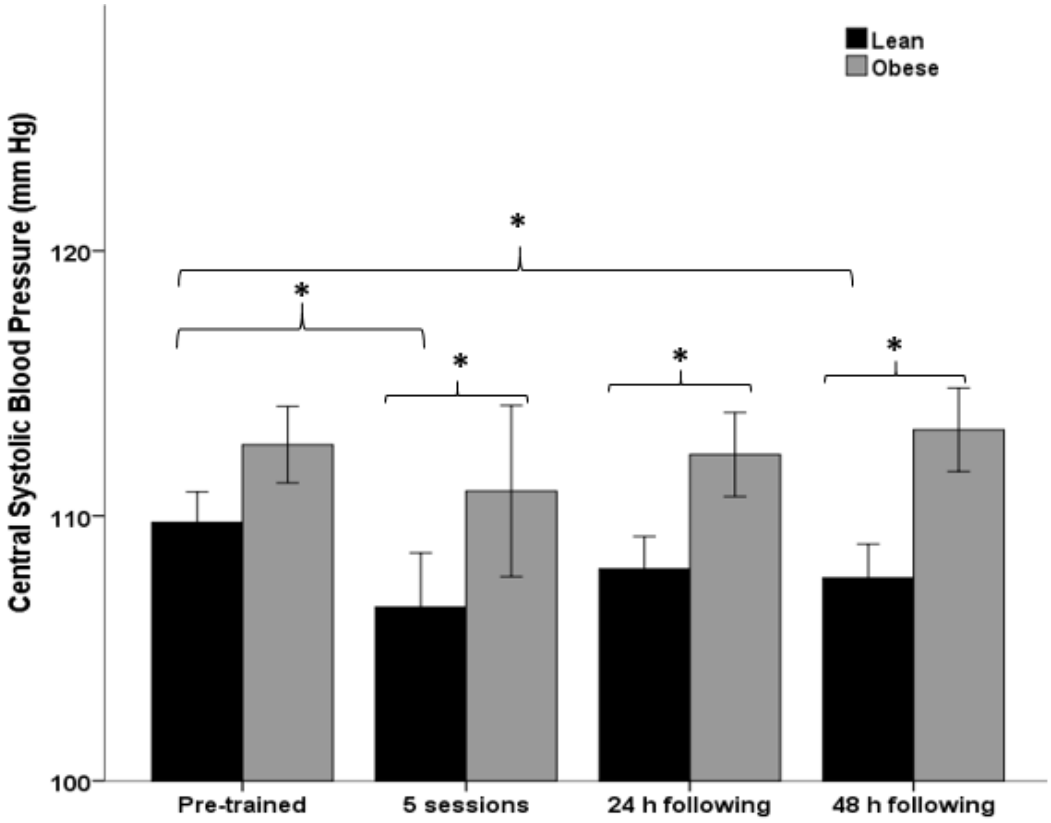


Figure 13. Average central systolic blood pressure (mm Hg) at rest when subjects were pre-trained, before the 6th exercise session, 24 and 48 h following the 6th exercise session for lean PHTN and obese PHTN. *Represents significantly different from baseline ($P < 0.05$). Error bar +/- 1 SE

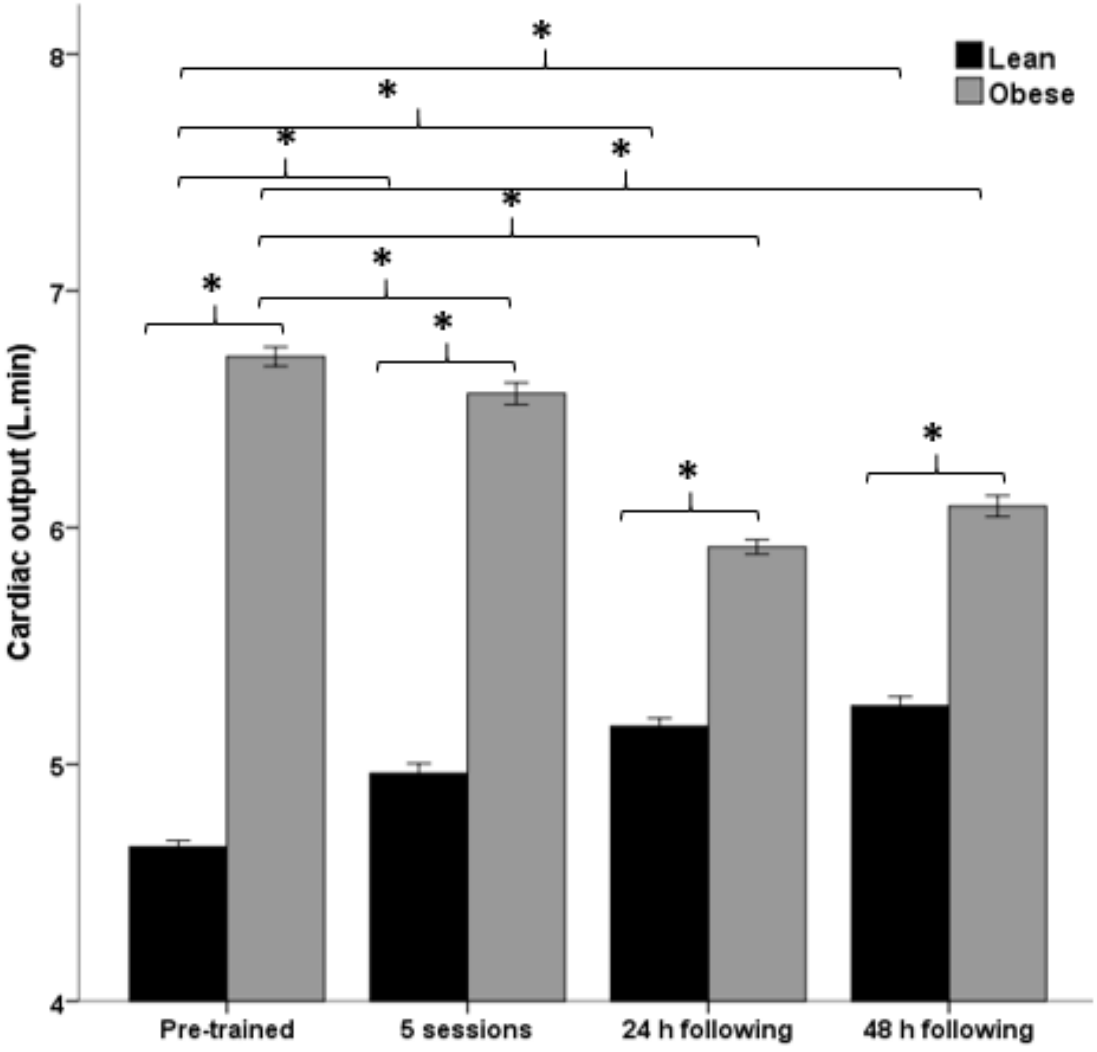


Figure 14. Average cardiac output (L/min) at rest when subjects were pre-trained, before the 6th exercise session, 24 and 48 h following the 6th exercise session for lean PHTN and obese PHTN. *($P < 0.05$). Error bar +/- 1 SE

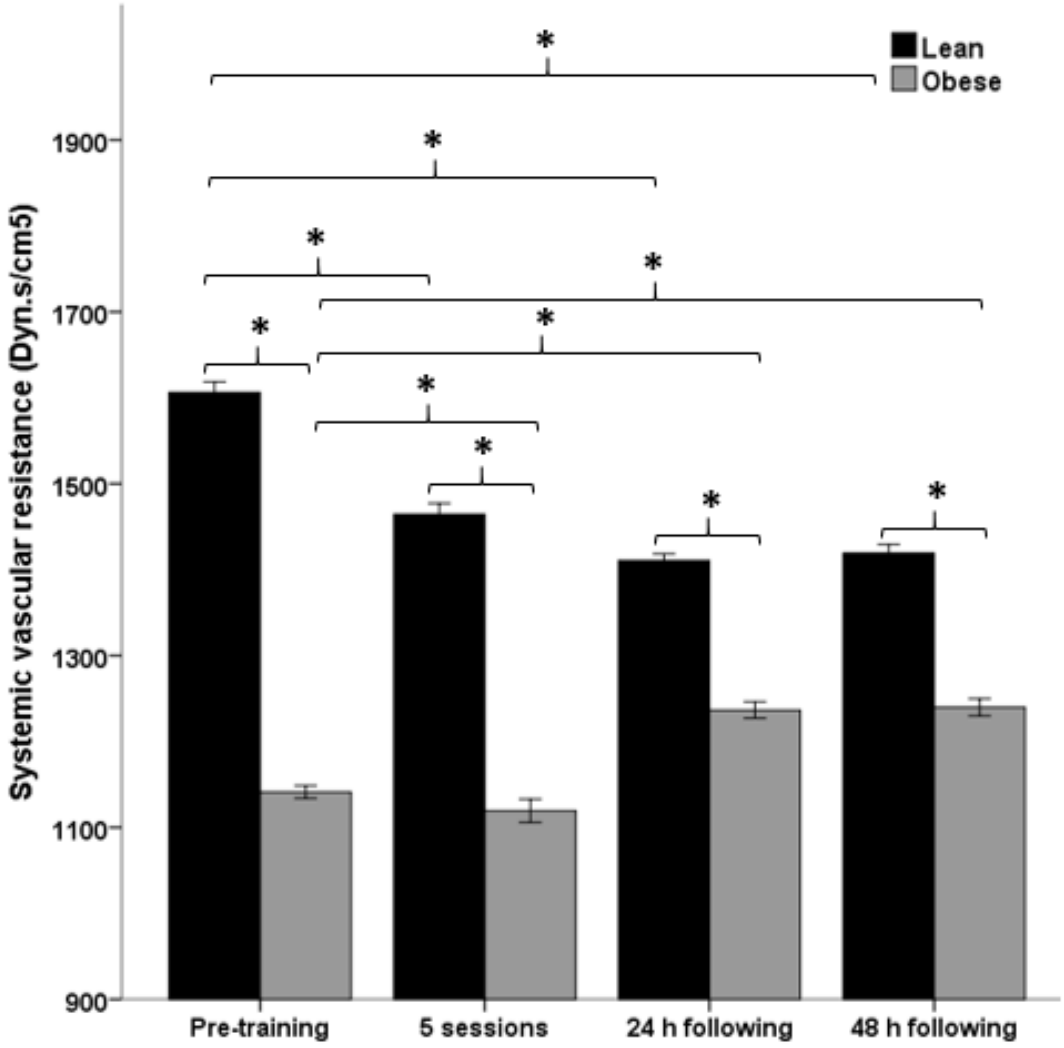


Figure 15. Average SVR (Dyn.s/cm^5) at rest when subjects were pre-trained, before the 6th exercise session, 24 and 48 h following the 6th exercise session for lean PHTN and obese PHTN. *(P < 0.05). Error bar +/- 1 SE

Predictive power of PEH. Figure 16 shows a significant association between the change in BSBP following acute exercise and the change in BSBP 48 h following the last exercise session (R = .577, P = 0.019). There was only a trend for a significant association between change in BSBP 24 h following last exercise session and change in BSBP following acute exercise (R= .380, P = 0.147).

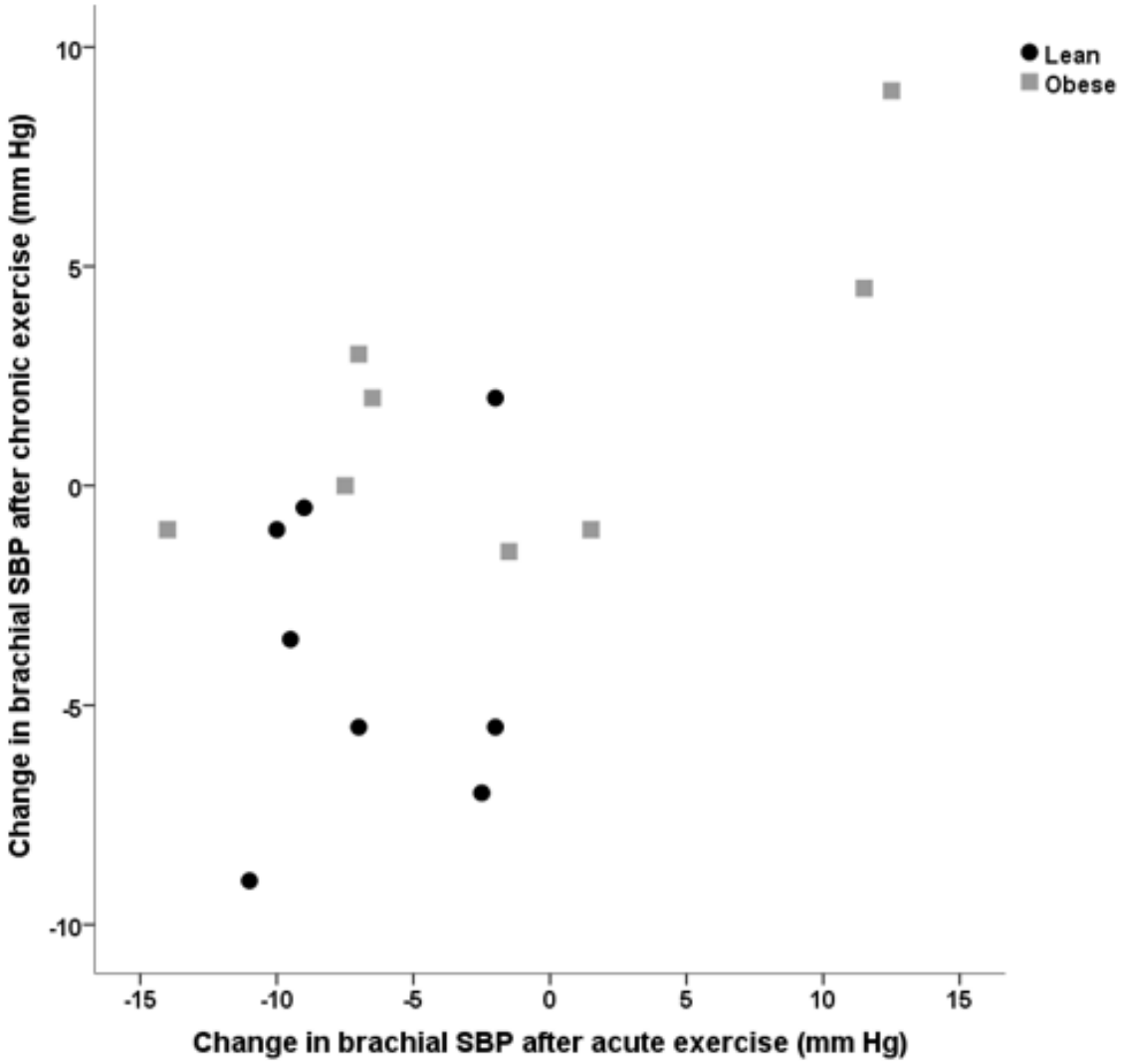


Figure 16. Pearson correlation between the change in BSBP following acute exercise compared to the change in BSBP following chronic exercise (48 h following the 6th exercise session).

CHAPTER FIVE

DISCUSSION

The primary aim of this study was to assess the impact of body phenotype on brachial BP and other central and peripheral hemodynamics in response to both acute and chronic exercise. The main finding of this study was that PHTN men with a lean phenotype experience significant PEH, while obese PHTN men experienced increased BP acutely following exercise. It was also found that the acute BP response to exercise foreshadowed what occurred in response to the short term training program. Our work corroborates previous research showing associations between the acute and chronic exercise response (76). Indeed, in the current study, with all subjects pooled together, a significant association was observed between PEH and chronic training reductions on BSBP. Our research adds to what has been done by showing corresponding changes in CO and SVR.

An interesting finding from our study was the immediate post-exercise BP increase following the exercise session for both groups. Posture has known effects on BP, in the current study subjects were asked to immediately lie supine following exercise. The supine position more than likely caused an increase CO due to increased volume returning to the heart, thus driving BP higher for 15 minutes following the exercise session. Were our subject to have maintained a seated position this response more than likely would have not been see. Even with this immediate increased BP, pressure still fell below baseline for the lean group.

The observation that Ci, Svi, and SVRi, showed no differences between group at rest while CO, SV, and SVR did show differences between groups further support our

study design, suggesting that hemodynamic differences between our groups were likely dependent on body mass. These resting hemodynamic differences between our groups, namely greater CO in the obese and increased SVR in the lean, have been documented by prior research (95, 131) and may help explain the divergent acute and chronic training responses seen. As a consequence of reduced SVR, obese HTN subjects have been considered hemodynamically "younger" than lean HTN subjects. Paradoxically, studies suggest obese HTN individuals may suffer from *fewer* cardiovascular events when compared to their lean HTN counterparts (91, 100, 135, 220). The precise theory as to why obese HTN individuals may be protected from cardiovascular events, namely a reduced SVR, may be the exact reason they did not respond favorably to exercise within the current trial.

In the majority of cases, indices of systemic and regional resistance are reduced below pre-exercise values during the PEH period (122). Conversely, CO is most often elevated during the post-exercise period (71). However, in different populations this may not be the case. It has been documented in elderly men, that post-exercise SVR may actually increase (64). Also, in endurance trained men CO has shown to decrease below pre-exercise values but not in women (182). Except in endurance trained men (182), stroke volume remains unchanged during the PEH period following exercise (72). This leads to the understanding that the mechanisms for PEH are different in heterogeneous populations. Both lean and obese PHTN men responded to acute exercise with an increase in CO, primarily due to increased HR, and decreased SVR. The driving force behind acute BP reductions to exercise is a reduction in SVR. During exercise at 6 METS for example, SVR has been predicted to fall to < 50% of resting levels (78). It

seems plausible that counter regulatory mechanisms would be evoked if SVR decreased too much to maintain cerebral blood flow. Indeed, acute cardiovascular collapse associated with loss of SVR is well recognized in many scenarios. In our study, obese PHTN men experienced a mere 75 Dyn·s/cm^5 reduction compared to a 224 Dyn·s/cm^5 reduction in lean PHTN men. However, lean PHTN men had a significantly higher resting SVR when compared to the obese.

A strength of our study was the additional measurements of central BP and central arterial stiffness. Central BP is not only effected by CO and SVR, but also by measures of central arterial stiffness, pressure waveform, waveform timing, and waveform magnitude (87). Because of this, changes in central BP and peripheral BP may not mimic each other. At rest, there were no differences between groups on BSBP (126 mm Hg vs 126 mm Hg, P = 0.976) but a trend for higher CSBP (113 mm Hg vs 110 mm Hg, P = 0.123) with the obese was seen. This is clinically relevant as central BP has been highlighted as a stronger measure than peripheral BP on predicting adverse cardiovascular outcomes (90, 171, 214).

It has previously been shown that the obese are more likely to have increased arterial stiffness independent of peripheral BP levels (176). This association may not be owing to obesity *per se* but central adiposity (51, 52). As an indicator of obesity, we not only used BMI > 30 kg/m^2, but also a waist circumference > 94 cm. There were significant group differences on measures of visceral adiposity at rest, and visceral fat was correlated with resting brachial and central BP in addition to all measures of arterial stiffness. Our obese subjects had significantly increased measures of Ap and Aix at rest when compared lean subjects. Although PWV was not statistically increased in the obese

group, this is more than likely a matter of sample size, not clinical significance. The .6 m/s increase in PWV within our PHTN obese compared to the PHTN lean has been associated with an 8% increase in CV events and a 9% increase in CV mortality (7). These differences between groups are also clinically relevant as it is now understood that central arterial stiffness precedes the development of HTN (94, 223).

The precise mechanisms that underlie the BP reduction in response to chronic exercise are not completely clear (23) owing to the complex etiology of HTN and dissimilarities across heterogeneous populations (23). Clearly to achieve a peripheral BP reduction in response to exercise, either CO, SVR or a combination of both, must decrease. Lean PHTN men saw significant reductions in both brachial and central SBP insomuch that following exercise training there were significant between group differences for both BSBP and CSBP. Obese PHTN men saw no such reductions. The reductions in BP for the lean group were accompanied with increased resting CO that was offset by the magnitude of reduction in resting SVR. Obese PHTN men responded in a divergent manner with a decreased resting CO and increased resting SVR following our exercise training program. This is congruent with previous literature showing that in response to aerobic exercise BP is reduced primarily due to decreased SVR (32).

Hemodynamic response to acute exercise changed in response to the subjects trained state. For obese PHTN men, there was a significant training status by time interaction for CO due to a greater decrease in SV acutely following exercise in a trained state compared to untrained. Obese PHTN also has a significant training status by time interaction for SVR insomuch that SVR did not decrease in response to acute exercise when in a trained state as it did in an untrained state. The trained acute response to

exercise mimicked the chronic adaptations seen in obese PHTN men, i.e. increased resting SVR and decreased resting CO.

Lean PHTN men witnessed a significant training status by time interactions for BSBP and CSBP insomuch that both acutely increased following exercise in the trained state. However, resting BP values for both central and peripheral SBP, as well as SVR were also significantly reduced from the pre-trained, pre-exercise resting values. It has been shown that pre-exercise resting BP is one of the strongest predictors of PEH. In fact, lean PHTN SVR achieved a lower absolute level when in a trained state compared to an untrained. Figure 11 shows that when excluding baseline BP, the response to exercise in a trained or untrained state is not statistically different.

The lack of reduction in central arterial stiffness values in response to aerobic training in either group is in accordance with prior literature. A 2014 meta-analysis (7) established that aerobic training caused greater reductions in peripheral arteries (brachial-ankle PWV) than with central arteries (cf-PWV) and those with stiffer arteries (PWV >8 m/s) saw greatest reductions in PWV. In our study central arterial stiffness was measured and our group of men had values of 6 m/s for lean and 6.6 m/s for obese. In addition, training that lasted longer than 10-weeks showed the best benefit on PWV, while ours lasted merely two.

The divergent findings between obese and lean PHTN in response to acute and chronic exercise cannot be explained beyond the hemodynamic properties that were measured in this study, namely SVR. It has been hypothesized that dysfunctional adipose tissue cause changes in secretion of adiponectin and leptin that could negatively impact SVR and sympathetic nervous system activity (61, 152). It has also been shown that

obesity increases renal sodium absorption due to increased sympathetic nervous system activity (69). These do not however explain why SVR increased in response to exercise training while SV decreased in obese PHTN males.

A strength of our study was the use of activity monitors to control for outside physical activity behaviors that may influence our results. There was no difference at rest or over the course of the three-week device-wearing period for energy expenditure or steps taken. The lean group had a significantly increased time spent in moderate activity by approximately 14 – 24 min/day and a significantly increased level of vigorous activity by about 1 – 4 min/day. This is not likely to affect the study outcomes. The subjects showed consistent physical activity behavior over the course of the baseline period and study intervention. The Sensewear device has also been shown to overestimate time spend in moderate activity (13). We also showed that measured fitness levels between group were not significantly different, confirming the sedentary nature of our subjects.

Our study is not without weaknesses. The outcomes measured are impacted by a multitude of factors, one being diet and fluid intake. Although diet records were given to the subjects to record dinner the night before and breakfast the morning of measurement visits, it is possible that subjects were inconsistent with diet intake. Subjects were asked to monitor fluid intake by consuming liquids from a bottle of a known quantity and to keep this quantity the same for each measurement visit. The integrity of this request relied with the subjects to comply. We also did not measure other factors associated with BP change such as catecholamines, sympathetic nervous system activation, renin aldosterone angiotensin system, or adipokines that could give further insight into phenotypic differences in response to exercise. For example, A 2012 paper by Halliwill

et al. (70) indicated that much of the PEH can be explained by histaminergic vasodilation, primarily due to the H1 and H2 receptors within the muscle. Combined H1 and H2 receptor antagonism reduced post-exercise vasodilation by roughly 80% and reduced PEH by 65% (70). To the authors knowledge there is no research illustrating possible differences between obese and lean on histaminergic activation. Future studies need to be designed and conducted to measure more precisely the mechanisms responsible for SVR findings in our study.

In conclusion, upwards of 25% of those who engage in an exercise program with the goal of decreasing BP are considered "non-responders" (17). It has been found that 12% of people actually *increase* BP (> 10 mm Hg) in response to exercise training (16). These data illustrate the critical need to identify factors that explain the heterogeneity of exercise response on BP. In the current study, every lean subject, except one (see figure 16), had a favorable brachial SBP response to chronic exercise raining. Only one obese subject had a training brachial SBP reduction. Considering body phenotype may be a simple way to predict the efficacy of an aerobic exercise program with the goal to reduce BP. This study should be considered as a pilot study and future research with increased sample sizes that could explore why body size may affect BP response to exercise need to be conducted.

References

1. Adji A, Hirata K, Hoegler S, O'Rourke MF. Noninvasive pulse waveform analysis in clinical trials: similarity of two methods for calculating aortic systolic pressure. *Am J Hypertens*. 2007; 20(8):917-22.

2. Agata J, Masuda A, Takada M, et al. High plasma immunoreactive leptin level in essential hypertension. *Am J Hypertens*. 1997; 10(10 Pt 1):1171-4.

3. American Heart Association. *Overweight andObesity Statistics - 2009 Update.*; 2009.

4. Anderson TJ, Gerhard MD, Meredith IT, et al. Systemic nature of endothelial dysfunction in atherosclerosis. *Am J Cardiol*. 1995; 75(6):71B-4B.

5. Angadi SS, Bhammar DM, Gaesser GA. Postexercise Hypotension After Continuous, Aerobic Interval, and Sprint Interval Exercise. *J Strength Cond Res*. 2015; 29(10):2888-93.

6. Angadi SS, Weltman A, Watson-Winfield D, et al. Effect of fractionized vs continuous, single-session exercise on blood pressure in adults. *J Hum Hypertens*. 2010; 24(4):300-2.

7. Ashor AW, Lara J, Siervo M, Celis-Morales C, Mathers JC. Effects of exercise modalities on arterial stiffness and wave reflection: a systematic review and meta-analysis of randomized controlled trials. . 2014.

8. Barbier P, Alioto G, Guazzi MD. Left atrial function and ventricular filling in hypertensive patients with paroxysmal atrial fibrillation. *J Am Coll Cardiol*. 1994; 24(1):165-70.

9. Barrett-Connor E, Khaw KT. Is hypertension more benign when associated with obesity? *Circulation*. 1985; 72(1):53-60.

10. Bassett DR,Jr, Howley ET, Thompson DL, et al. Validity of inspiratory and expiratory methods of measuring gas exchange with a computerized system. *J Appl Physiol (1985)*. 2001; 91(1):218-24.

11. Bender R, Jockel KH, Richter B, Spraul M, Berger M. Body weight, blood pressure, and mortality in a cohort of obese patients. *Am J Epidemiol*. 2002; 156(3):239-45.

12. Bhammar DM, Angadi SS, Gaesser GA. Effects of fractionalized and continuous exercise on 24-h ambulatory blood pressure. *MSSE*. 2012; 44(12):2270-76.

13. Bhammar DM, Sawyer BJ, Tucker WJ, Lee J, Gaesser GA. Validity of SenseWear® Armband v5. 2 and v2. 2 for estimating energy expenditure. *J Sports Sci*. 2016:1-9.

14. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of blood pressure lowering on cardiovascular risk according to baseline body-mass index: a meta-analysis of randomised trials. *The Lancet*. 2015; 385(9971):867-74.

15. Bloom E, Reed D, Yano K, MacLean C. Does obesity protect hypertensives against cardiovascular disease? *JAMA*. 1986; 256(21):2972-5.

16. Bouchard C, Blair SN, Church TS, et al. Adverse metabolic response to regular exercise: is it a rare or common occurrence. *PLoS One*. 2012; 7(5):e37887.

17. Bouchard C, Rankinen T. Individual differences in response to regular physical activity. *Med Sci Sports Exerc*. 2001; 33(6 Suppl):S446,51; discussion S452-3.

18. Brook RD, Bard RL, Rubenfire M, Ridker PM, Rajagopalan S. Usefulness of visceral obesity (waist/hip ratio) in predicting vascular endothelial function in healthy overweight adults. *Am J Cardiol*. 2001; 88(11):1264-9.

19. Brown MD. Exercise and coronary vascular remodelling in the healthy heart. *Exp Physiol*. 2003; 88(05):645-58.

20. Busse R, Fleming I. Regulation of endothelium-derived vasoactive autacoid production by hemodynamic forces. *Trends Pharmacol Sci*. 2003; 24(1):24-9.

21. Cambien F, Chretien JM, Ducimetiere P, Guize L, Richard JL. Is the relationship between blood pressure and cardiovascular risk dependent on body mass index? *Am J Epidemiol*. 1985; 122(3):434-42.

22. Canoy D, Luben R, Welch A, et al. Fat distribution, body mass index and blood pressure in 22 090 men and women in the Norfolk cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Norfolk) study. *J Hypertens*. 2004; 22(11):2067-74.

23. Cardoso CG,Jr, Gomides RS, Queiroz AC, et al. Acute and chronic effects of aerobic and resistance exercise on ambulatory blood pressure. *Clinics (Sao Paulo)*. 2010; 65(3):317-25.

24. Carman WJ, Barrett-Connor E, Sowers M, Khaw KT. Higher risk of cardiovascular mortality among lean hypertensive individuals in Tecumseh, Michigan. *Circulation*. 1994; 89(2):703-11.

25. Cavelaars M, Tulen JH, van Bemmel JH, Mulder PG, van den Meiracker, Anton H. Haemodynamic responses to physical activity and body posture during everyday life. *J Hypertens*. 2004; 22(1):89-96.

26. Charloux A, Lonsdorfer-Wolf E, Richard R, et al. A new impedance cardiograph device for the non-invasive evaluation of cardiac output at rest and during exercise: comparison with the "direct" Fick method. *Eur J Appl Physiol*. 2000; 82(4):313-20.

27. Chen KH, Henderson VW, Stolwyk RJ, Dennerstein L, Szoeke C. Prehypertension in midlife is associated with worse cognition a decade later in middle-aged and older women. *Age Ageing*. 2015; 44(3):439-45.

28. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003; 42(6):1206-52.

29. Chrostowska M, Szczech R, Narkiewicz K. Antihypertensive therapy in the obese hypertensive patient. *Curr Opin Nephrol Hypertens*. 2006; 15(5):487-92.

30. Chrysant SG, Chrysant GS. New insights into the true nature of the obesity paradox and the lower cardiovascular risk. *Journal of the American Society of Hypertension*. 2013; 7(1):85-94.

31. Colussi G, Catena C, Lapenna R, Nadalini E, Chiuch A, Sechi LA. Insulin resistance and hyperinsulinemia are related to plasma aldosterone levels in hypertensive patients. *Diabetes Care*. 2007; 30(9):2349-54.

32. Cornelissen VA, Fagard RH. Effects of endurance training on blood pressure, blood pressure-regulating mechanisms, and cardiovascular risk factors. *Hypertension*. 2005; 46(4):667-75.

33. Cowley Jr AW. Long-term control of arterial blood pressure. *Physiol Rev*. 1992; 72(1):231-300.

34. Crandall CG. Heat stress and baroreflex regulation of blood pressure. *Med Sci Sports Exerc*. 2008; 40(12):2063-70.

35. Creager MA, Beckman JA, Loscalzo J. *Vascular Medicine: A Companion to Braunwald's Heart Disease.* Elsevier Health Sciences; 2012.

36. Crews DC, Plantinga LC, Miller ER,3rd, et al. Prevalence of chronic kidney disease in persons with undiagnosed or prehypertension in the United States. *Hypertension*. 2010; 55(5):1102-9.

37. Danchin N, Benetos A, Lopez-Sublet M, et al. Aortic pulse pressure is related to the presence and extent of coronary artery disease in men undergoing diagnostic coronary angiography: a multicenter study. *Am J Hypertens*. 2004; 17(2):129-33.

38. Dawber TR. *The Framingham Study: The Epidemiology of Atherosclerotic Disease.* Harvard University Press Cambridge, MA:; 1980.

39. Deague JA, Wilson CM, Grigg LE, Harrap SB. Increased left ventricular mass is not associated with impaired left ventricular diastolic filling in normal individuals. *J Hypertens*. 2000; 18(6):757-62.

40. Delp MD, Laughlin MH. Time course of enhanced endothelium-mediated dilation in aorta of trained rats. *Med Sci Sports Exerc*. 1997; 29(11):1454-61.

41. Dohi Y, Thiel MA, Buhler FR, Luscher TF. Activation of endothelial L-arginine pathway in resistance arteries. Effect of age and hypertension. *Hypertension*. 1990; 16(2):170-9.

42. Dorresteijn J, Visseren F, Spiering W. Mechanisms linking obesity to hypertension. *Obesity Reviews*. 2012; 13(1):17-26.

43. Duarte D, Santos-Araújo C, Leite-Moreira AF. Hypertension and angiogenesis in the aging kidney: A review. *Arch Gerontol Geriatr*. 2011; 52(3):e93-e102.

44. Dunbar JC, Hu Y, Lu H. Intracerebroventricular leptin increases lumbar and renal sympathetic nerve activity and blood pressure in normal rats. *Diabetes*. 1997; 46(12):2040-3.

45. El Assar M, Ruiz de Adana J, Angulo J, Pindado Martinez ML, Hernandez Matias A, Rodríguez-Mañas L. Preserved endothelial function in human obesity in the absence of insulin resistance. *J Transl Med*. 2013; 11:263.

46. Elias PK, Elias MF, Robbins MA, Budge MM. Blood pressure-related cognitive decline: does age make a difference? *Hypertension*. 2004; 44(5):631-6.

47. Elliott P, Shipley M, Jarrett R. Obesity and hypertension. *The Lancet*. 1988; 331(8592):995.

48. Engeli S, Bohnke J, Gorzelniak K, et al. Weight loss and the renin-angiotensin-aldosterone system. *Hypertension*. 2005; 45(3):356-62.

49. Epstein FH, Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med*. 1999; 340(2):115-26.

50. Ezzati M, Vander Hoorn S, Lopez AD, et al. Comparative quantification of mortality and burden of disease attributable to selected risk factors. *Global burden of disease and risk factors*. 2006; 2:241-396.

51. Fantin F, Rossi AP, Cazzadori M, et al. Central and peripheral fat and subclinical vascular damage in older women. *Age Ageing*. 2013; 42(3):359-65.

52. Ferreira I, Snijder MB, Twisk JW, et al. Central fat mass versus peripheral fat and lean mass: opposite (adverse versus favorable) associations with arterial stiffness? The Amsterdam Growth and Health Longitudinal Study. *The Journal of Clinical Endocrinology & Metabolism*. 2004; 89(6):2632-9.

53. Forjaz C, Cardoso C, Rezk C, Santaella D, Tinucci T. Postexercise hypotension and hemodynamics: the role of exercise intensity. *J Sports Med Phys Fitness*. 2004; 44(1):54-62.

54. Frohlich ED, Apstein C, Chobanian AV, et al. The heart in hypertension. *N Engl J Med*. 1992; 327(14):998-1008.

55. Frohlich ED. State of the Art lecture. Risk mechanisms in hypertensive heart disease. *Hypertension*. 1999; 34(4 Pt 2):782-9.

56. Frohlich ED, Messerli FH, Reisin E, Dunn FG. The problem of obesity and hypertension. *Hypertension*. 1983; 5(5 Pt 2):III71-8.

57. Fuchs FD. Prehypertension: the rationale for early drug therapy. *Cardiovascular therapeutics*. 2010; 28(6):339-43.

58. Garrison RJ, Kannel WB, Stokes J, Castelli WP. Incidence and precursors of hypertension in young adults: the Framingham Offspring Study. *Prev Med*. 1987; 16(2):235-51.

59. Goldbourt U, Holtzman E, Cohen-Mandelzweig L, Neufeld HN. Enhanced risk of coronary heart disease mortality in lean hypertensive men. *Hypertension*. 1987; 10(1):22-8.

60. Goodfriend TL, Kelley DE, Goodpaster BH, Winters SJ. Visceral obesity and insulin resistance are associated with plasma aldosterone levels in women. *Obes Res*. 1999; 7(4):355-62.

61. Grassi G, Seravalle G, Cattaneo BM, et al. Sympathetic activation in obese normotensive subjects. *Hypertension*. 1995; 25(4 Pt 1):560-3.

62. Green DJ, Maiorana A, O'Driscoll G, Taylor R. Effect of exercise training on endothelium-derived nitric oxide function in humans. *J Physiol (Lond)*. 2004; 561(1):1-25.

63. Grossman E, Oren S, Garavaglia GE, Schmieder R, Messerli FH. Disparate hemodynamic and sympathoadrenergic responses to isometric and mental stress in essential hypertension. *Am J Cardiol*. 1989; 64(1):42-4.

64. Hagberg JM, Montain SJ, Martin WH,3rd. Blood pressure and hemodynamic responses after exercise in older hypertensives. *J Appl Physiol*. 1987; 63(1):270-6.

65. Hagberg JM, Park JJ, Brown MD. The role of exercise training in the treatment of hypertension: an update. *Sports Med*. 2000; 30(3):193-206.

66. Hajer GR, van Haeften TW, Visseren FL. Adipose tissue dysfunction in obesity, diabetes, and vascular diseases. *Eur Heart J*. 2008; 29(24):2959-71.

67. Hajjar I, Kotchen JM, Kotchen TA. Hypertension: trends in prevalence, incidence, and control. *Annu Rev Public Health*. 2006; 27:465-90.

68. HALL J. RENAL AND CARDIOVASCULAR MECHANISMS OF HYPERTENSION IN OBESITY. In: *CIRCULATION*. AMER HEART ASSOC 7272 GREENVILLE AVENUE, DALLAS, TX 75231-4596; 1992, p. S5-.

69. Hall JE, Brands MW, Dixon WN, Smith MJ,Jr. Obesity-induced hypertension. Renal function and systemic hemodynamics. *Hypertension*. 1993; 22(3):292-9.

70. Halliwill JR, Buck TW, Lacewell AN, Romero SA. Postexercise hypotension and sustained postexercise vasodilatation: what happens after we exercise. *Exp Physiol*. 2012; 00(00):1-12.

71. Halliwill JR. Mechanisms and clinical implications of post-exercise hypotension in humans. *Exerc Sport Sci Rev*. 2001; 29(2):65-70.

72. Halliwill JR, Minson CT, Joyner MJ. Effect of systemic nitric oxide synthase inhibition on postexercise hypotension in humans. *J Appl Physiol (1985)*. 2000; 89(5):1830-6.

73. Hambrecht R, Adams V, Erbs S, et al. Regular physical activity improves endothelial function in patients with coronary artery disease by increasing phosphorylation of endothelial nitric oxide synthase. *Circulation*. 2003; 107(25):3152-8.

74. Hamilton W. The patterns of the arterial pressure pulse. *American Journal of Physiology--Legacy Content*. 1944; 141(2):235-41.

75. Hart EC, Charkoudian N, Wallin BG, Curry TB, Eisenach J, Joyner MJ. Sex and ageing differences in resting arterial pressure regulation: the role of the β-adrenergic receptors. *J Physiol (Lond)*. 2011; 589(21):5285-97.

76. Hecksteden A, Grutters T, Meyer T. Association between postexercise hypotension and long-term training-induced blood pressure reduction: a pilot study. *Clin J Sport Med*. 2013; 23(1):58-63.

77. Hecksteden A, Grutters T, Meyer T. Association between postexercise hypotension and long-term training-induced blood pressure reduction: a pilot study. *Clin J Sport Med*. 2013; 23(1):58-63.

78. Hogan TS. Exercise-induced reduction in systemic vascular resistance: A covert killer and an unrecognised resuscitation challenge? *Med Hypotheses*. 2009; 73(4):479-84.

79. Huang Y, Su L, Cai X, et al. Association of all-cause and cardiovascular mortality with prehypertension: a meta-analysis. *Am Heart J*. 2014; 167(2):160,168. e1.

80. Huang Y, Cai X, Zhang J, et al. Prehypertension and Incidence of ESRD: a systematic review and meta-analysis. *Am J Kidney Dis*. 2014; 63(1):76-83.

81. Huang Y, Su L, Cai X, et al. Association of all-cause and cardiovascular mortality with prehypertension: a meta-analysis. *Am Heart J*. 2014; 167(2):160,168.e1.

82. Huang Y, Wang S, Cai X, et al. Prehypertension and incidence of cardiovascular disease: a meta-analysis. *BMC Med*. 2013; 11:177,7015-11-177.

83. Huang Y, Cai X, Li Y, et al. Prehypertension and the risk of stroke: A meta-analysis. *Neurology*. 2014.

84. Hwang M, Yoo J, Kim H, et al. Validity and reliability of aortic pulse wave velocity and augmentation index determined by the new cuff-based SphygmoCor Xcel. *J Hum Hypertens*. 2014; 28(8):475-81.

85. Inaba Y, Chen JA, Bergmann SR. Prediction of future cardiovascular outcomes by flow-mediated vasodilatation of brachial artery: a meta-analysis. *The international journal of cardiovascular imaging*. 2010; 26(6):631-40.

86. Ingelsson E, Pencina MJ, Tofler GH, et al. Multimarker approach to evaluate the incidence of the metabolic syndrome and longitudinal changes in metabolic risk factors: the Framingham Offspring Study. *Circulation*. 2007; 116(9):984-92.

87. Izzo JL,Jr. Arterial stiffness and the systolic hypertension syndrome. *Curr Opin Cardiol*. 2004; 19(4):341-52.

88. James PA, Oparil S, Carter BL, et al. 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2013.

89. Jankowski P, Kawecka-Jaszcz K, Bryniarski L, et al. Fractional diastolic and systolic pressure in the ascending aorta are related to the extent of coronary artery disease. *Am J Hypertens*. 2004; 17(8):641-6.

90. Jankowski P, Kawecka-Jaszcz K, Czarnecka D, et al. Pulsatile but not steady component of blood pressure predicts cardiovascular events in coronary patients. *Hypertension*. 2008; 51(4):848-55.

91. Johnson AL, Cornoni JC, Cassel JC, Tyroler HA, Heyden S, Hames CG. Influence of race, sex and weight on blood pressure behavior in young adults. *Am J Cardiol*. 1975; 35(4):523-30.

92. Jones H, Pritchard C, George K, Edwards B, Atkinson G. The acute post-exercise response of blood pressure varies with time of day. *Eur J Appl Physiol*. 2008; 104:481-89.

93. Jones H, Pritchard C, George K, Edwards B, Atkinson G. The acute post-exercise response of blood pressure varies with time of day. *Eur J Appl Physiol*. 2008; 104(3):481-9.

94. Kaess BM, Rong J, Larson MG, et al. Aortic stiffness, blood pressure progression, and incident hypertension. *JAMA*. 2012; 308(9):875-81.

95. Kalil GZ, Haynes WG. Sympathetic nervous system in obesity-related hypertension: mechanisms and clinical implications. *Hypertension Research*. 2012; 35(1):4-16.

96. Kannel W, Wolf P, Garrison R. Some risk factors related to the annual incidence of cardiovascular disease and death in pooled repeated biennial measurements: Framingham Heart Study, 30 year follow-up. *The Framingham Study: An Epidemiological Investigation of Cardiovascular Disease*. 1987.

97. Kannel WB, Dannenberg AL, Levy D. Population implications of electrocardiographic left ventricular hypertrophy. *Am J Cardiol*. 1987; 60(17):85-93.

98. Kannel WB, Wolf PA, Verter J, McNamara PM. Epidemiologic assessment of the role of blood pressure in stroke: the Framingham study. *JAMA*. 1970; 214(2):301-10.

99. Kannel WB, Zhang T, Garrison RJ. Is obesity-related hypertension less of a cardiovascular risk? The Framingham Study. *Am Heart J*. 1990; 120(5):1195-201.

100. Kannel WB, Brand N, Skinner JJ,Jr, Dawber TR, McNamara PM. The relation of adiposity to blood pressure and development of hypertension. The Framingham study. *Ann Intern Med*. 1967; 67(1):48-59.

101. Karamanoglu M, O'rourke M, Avolio A, Kelly R. An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man. *Eur Heart J*. 1993; 14(2):160-7.

102. Kazumi T, Kawaguchi A, Katoh J, Iwahashi M, Yoshino G. Fasting insulin and leptin serum levels are associated with systolic blood pressure independent of percentage body fat and body mass index. *J Hypertens*. 1999; 17(10):1451-5.

103. Kearney MT, Duncan ER, Kahn M, Wheatcroft SB. Insulin resistance and endothelial cell dysfunction: studies in mammalian models. *Exp Physiol*. 2008; 93(1):158-63.

104. Kiernan M, Schoffman D, Lee K, et al. The Stanford Leisure-Time Activity Categorical Item (L-Cat): a single categorical item sensitive to physical activity changes in overweight/obese women. *Int J Obes*. 2013; 37(12):1597-602.

105. Kim MJ, Lim NK, Park HY. Relationship between prehypertension and chronic kidney disease in middle-aged people in Korea: the Korean genome and epidemiology study. *BMC Public Health*. 2012; 12:960,2458-12-960.

106. Kingwell BA, Waddell TK, Medley TL, Cameron JD, Dart AM. Large artery stiffness predicts ischemic threshold in patients with coronary artery disease. *J Am Coll Cardiol*. 2002; 40(4):773-9.

107. Kiviniemi AM, Hautala AJ, Karjalainen JJ, et al. Acute post-exercise change in blood pressure and exercise training response in patients with coronary artery disease. *Frontiers in Physiology*. 2015; 5:526.

108. Landsberg L, Aronne LJ, Beilin LJ, et al. Obesity-related hypertension: pathogenesis, cardiovascular risk, and treatment--a position paper of the The Obesity Society and The American Society of Hypertension. *Obesity (Silver Spring)*. 2013; 21(1):8-24.

109. Laurent S, Boutouyrie P, Lacolley P. Structural and genetic bases of arterial stiffness. *Hypertension*. 2005; 45(6):1050-5.

110. Laurent S, Cockcroft J, Van Bortel L, et al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*. 2006; 27(21):2588-605.

111. Lavie CJ, Milani RV. Obesity and cardiovascular disease: the hippocrates paradox?*. *J Am Coll Cardiol*. 2003; 42(4):677-9.

112. Lavie CJ, Milani RV, Ventura HO, Cardenas GA, Mehra MR, Messerli FH. Disparate effects of left ventricular geometry and obesity on mortality in patients with preserved left ventricular ejection fraction. *Am J Cardiol*. 2007; 100(9):1460-4.

113. Lee CMY, Huxley RR, Wildman RP, Woodward M. Indices of abdominal obesity are better discriminators of cardiovascular risk factors than BMI: a meta-analysis. *J Clin Epidemiol*. 2008; 61(7):646-53.

114. Levy D. Left ventricular hypertrophy. *Drugs*. 1988; 35(5):1-5.

115. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med*. 1990; 322(22):1561-6.

116. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002; 360(9349):1903-13.

117. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *The lancet*. 2013; 380(9859):2224-60.

118. Lind AR, Sutton, Ventricular Function George C, Prewitt TA, et al. Editorial. Cardiovascular responses to static exercise (isometrics, anyone?). *Circulation*. 1970; 41:I73.

119. Littmann D. The natural history of congestive heart failure. *N Engl J Med*. 1971; 285(26):1481-2.

120. Liu S, Goodman J, Nolan R, Lacombe S, Thomas SG. Blood pressure responses to acute and chronic exercise are related in prehypertension. *Med Sci Sports Exerc*. 2012; 44(9):1644-52.

121. London GM, Blacher J, Pannier B, Guerin AP, Marchais SJ, Safar ME. Arterial wave reflections and survival in end-stage renal failure. *Hypertension*. 2001; 38(3):434-8.

122. MacDonald JR. Potential causes, mechanisms, and implications of post exercise hypotension. *J Hum Hypertens*. 2002; 16(4):225-36.

123. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Blood Press*. 2013; 22(4):193-278.

124. Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2007; 28(12):1462-536.

125. Mannion TC, Vita JA, Keaney JF,Jr, Benjamin EJ, Hunter L, Polak JF. Non-invasive assessment of brachial artery endothelial vasomotor function: the effect of cuff position on level of discomfort and vasomotor responses. *Vasc Med*. 1998; 3(4):263-7.

126. Marcus ML, Mueller TM, Eastham CL. Effects of short- and long-term left ventricular hypertrophy on coronary circulation. *Am J Physiol*. 1981; 241(3):H358-62.

127. McEniery CM, Hall IR, Qasem A, Wilkinson IB, Cockcroft JR. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). *J Am Coll Cardiol*. 2005; 46(9):1753-60.

128. McEniery CM, Wallace S, Mackenzie IS, et al. Endothelial function is associated with pulse pressure, pulse wave velocity, and augmentation index in healthy humans. *Hypertension*. 2006; 48(4):602-8.

129. Menotti A, Giampaoli S, Pasquali M, Seccareccia F, Stuart K. Prognosis of lean and fat hypertensives. *Cardiology*. 1988; 75(6):448-57.

130. Meredith IT, Jennings GL, Esler MD, et al. Time-course of the antihypertensive and autonomic effects of regular endurance exercise in human subjects. *J Hypertens*. 1990; 8(9):859-66.

131. Messerli FH, Sundgaard-Riise K, Reisin E, Dreslinski G, Dunn FG, Frohlich E. Disparate cardiovascular effects of obesity and arterial hypertension. *Am J Med*. 1983; 74(5):808-12.

132. Messerli FH, Sundgard-Rise K, Reisin E, et al. Left ventricular adaptation to obesity. *Am J Cardiol*. 1982; 49(4):977.

133. Messerli FH. Cardiovascular adaptations to obesity and arterial hypertension: detrimental or beneficial? *Int J Cardiol*. 1983; 3(1):94-7.

134. Metcalfe DD, Baram D, Mekori YA. Mast cells. *Physiol Rev*. 1997; 77(4):1033-80.

135. Mikhail N, Golub MS, Tuck ML. Obesity and hypertension. *Prog Cardiovasc Dis*. 1999; 42(1):39-58.

136. Millar-Craig M, Bishop C, Raftery E. Circadian variation of blood-pressure. *The Lancet*. 1978; 311(8068):795-7.

137. Mitchell GF, Hwang SJ, Vasan RS, et al. Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation*. 2010; 121(4):505-11.

138. Moker EA, Bateman LA, Kraus WE, Pescatello LS. The Relationship between the Blood Pressure Responses to Exercise following Training and Detraining Periods. . 2014.

139. Moncada S, Palmer RM, Higgs EA. Nitric oxide: physiology, pathophysiology, and pharmacology. *Pharmacol Rev*. 1991; 43(2):109-42.

140. Montero D, Roberts CK, Vinet A. Effect of aerobic exercise training on arterial stiffness in obese populations. *Sports Medicine*. 2014; 44(6):833-43.

141. Montero D, Roche E, Martinez-Rodriguez A. The impact of aerobic exercise training on arterial stiffness in pre-and hypertensive subjects: A systematic review and meta-analysis. *Int J Cardiol*. 2014; 173(3):361-8.

142. Murray A, Delaney T, Bell C. Rapid onset and offset of circulatory adaptations to exercise training in men. *J Hum Hypertens*. 2006; 20(3):193-200.

143. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. *JAMA*. 1999; 282(16):1523-9.

144. Myers MG, Cowley MA, Münzberg H. Mechanisms of leptin action and leptin resistance. *Annu Rev Physiol*. 2008; 70:537-56.

145. National Heart Lung and Blood Institute. *Systolic Blood Pressure Intervention Trial (SPRINT)*. 2011.

146. Neisius U, Bilo G, Taurino C, et al. Association of central and peripheral pulse pressure with intermediate cardiovascular phenotypes. *J Hypertens*. 2012; 30(1):67-74.

147. Neter JE, Stam BE, Kok FJ, Grobbee DE, Geleijnse JM. Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension*. 2003; 42(5):878-84.

148. Norton GR, Majane OH, Maseko MJ, et al. Brachial blood pressure-independent relations between radial late systolic shoulder-derived aortic pressures and target organ changes. *Hypertension*. 2012; 59(4):885-92.

149. O'Rourke MF, Staessen JA, Vlachopoulos C, Duprez D. Clinical applications of arterial stiffness; definitions and reference values. *American journal of hypertension*. 2002; 15(5):426-44.

150. Oda A, Taniguchi T, Yokoyama M. Leptin stimulates rat aortic smooth muscle cell proliferation and migration. *Kobe J Med Sci*. 2001; 47(3):141-50.

151. O'Rourke M. Mechanical principles in arterial disease. *Hypertension*. 1995; 26(1):2-9.

152. Ouchi N, Ohishi M, Kihara S, et al. Association of hypoadiponectinemia with impaired vasoreactivity. *Hypertension*. 2003; 42(3):231-4.

153. Palombo C, Kozakova M, Magagna A, et al. Early impairment of coronary flow reserve and increase in minimum coronary resistance in borderline hypertensive patients. *J Hypertens*. 2000; 18(4):453-9.

154. Pauca AL, O'Rourke MF, Kon ND. Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. *Hypertension*. 2001; 38(4):932-7.

155. Pescatello LS, Blanchard BE, Van Heest JL, Maresh CM, Gordish-Dressman H, Thompson PD. The metabolic syndrome and the immediate antihypertensive effects of aerobic exercise: a randomized control design. *BMC Cardiovasc Disord*. 2008; 8:12,2261-8-12.

156. Pescatello LS, Franklin BA, Fagard R, et al. American College of Sports Medicine position stand. Exercise and hypertension. *Med Sci Sports Exerc*. 2004; 36(3):533-53.

157. Pescatello LS, Franklin BA, Fagard R, et al. American College of Sports Medicine position stand. Exercise and hypertension. *Med Sci Sports Exerc*. 2004; 36(3):533-53.

158. Pescatello LS, Kulikowich JM. The aftereffects of dynamic exercise on ambulatory blood pressure. *Med Sci Sports Exerc*. 2001; 33(11):1855-61.

159. Phillips A, Shaper A. Relative weight and major ischaemic heart disease events in hypertensive men. *The Lancet*. 1989; 333(8645):1005-8.

160. Pluim BM, Zwinderman AH, van der Laarse A, van der Wall EE. The athlete's heart. A meta-analysis of cardiac structure and function. *Circulation*. 2000; 101(3):336-44.

161. Pooling Project Research Group. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: final report of the Pooling Project. *J Chronic Dis*. 1978; 31(4):201-306.

162. Pou KM, Massaro JM, Hoffmann U, et al. Visceral and subcutaneous adipose tissue volumes are cross-sectionally related to markers of inflammation and oxidative stress: the Framingham Heart Study. *Circulation*. 2007; 116(11):1234-41.

163. Rahmouni K, Morgan DA, Morgan GM, Mark AL, Haynes WG. Role of selective leptin resistance in diet-induced obesity hypertension. *Diabetes*. 2005; 54(7):2012-8.

164. Ras RT, Streppel MT, Draijer R, Zock PL. Flow-mediated dilation and cardiovascular risk prediction: a systematic review with meta-analysis. *Int J Cardiol*. 2013; 168(1):344-51.

165. Ratnasabapathy Y, Lawes CM, Anderson CS. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS). *Drugs Aging*. 2003; 20(4):241-51.

166. Reisin E, Hutchinson H. Obesity-hypertension: effects on the cardiovascular and renal system—the therapeutic approach. *Hypertension.Philadelphia: WB Saunders*. 1999:206-10.

167. Richard R, Lonsdorfer-Wolf E, Charloux A, et al. Non-invasive cardiac output evaluation during a maximal progressive exercise test, using a new impedance cardiograph device. *Eur J Appl Physiol*. 2001; 85(3-4):202-7.

168. Ritz E. Hypertension and kidney disease. *Clin Nephrol*. 2010; 74 Suppl 1:S39-43.

169. Robinson SC, Brucer M. Range of normal blood pressure: a statistical and clinical study of 11,383 persons. *Arch Intern Med*. 1939; 64(3):409-44.

170. Rockstroh JK, Schmieder RE, Schachinger H, Messerli FH. Stress response pattern in obesity and systemic hypertension. *Am J Cardiol*. 1992; 70(11):1035-9.

171. Roman MJ, Devereux RB, Kizer JR, et al. Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. *Hypertension*. 2007; 50(1):197-203.

172. Rowell LB, Brengelmann GL, Blackmon JR, Bruce RA, Murray JA. Disparities between aortic and peripheral pulse pressures induced by upright exercise and vasomotor changes in man. *Circulation*. 1968; 37(6):954-64.

173. Rumantir MS, Vaz M, Jennings GL, et al. Neural mechanisms in human obesity-related hypertension. *J Hypertens*. 1999; 17(8):1125-33.

174. Safar ME, Henry O, Meaume S. Aortic pulse wave velocity: an independent marker of cardiovascular risk. *Am J Geriatr Cardiol*. 2002; 11(5):295-304.

175. Safar ME, Blacher J, Pannier B, et al. Central pulse pressure and mortality in end-stage renal disease. *Hypertension*. 2002; 39(3):735-8.

176. Safar ME, Czernichow S, Blacher J. Obesity, arterial stiffness, and cardiovascular risk. *J Am Soc Nephrol*. 2006; 17(4 Suppl 2):S109-11.

177. SALANS AH, KATZ LN, GRAHAM GR, GORDON A, ELISBERG EI, GERBER A. A study of the central and peripheral arterial pressure pulse in man; correlation with simultaneously recorded electrokymograms. *Circulation*. 1951; 4(4):510-21.

178. Savage DD, Drayer JI, Henry WL, et al. Echocardiographic assessment of cardiac anatomy and function in hypertensive subjects. *Circulation*. 1979; 59(4):623-32.

179. Schmieder RE, Messerli FH. Hypertension and the heart. *J Hum Hypertens*. 2000; 14(10-11):597-604.

180. Schnabel R, Larson MG, Dupuis J, et al. Relations of inflammatory biomarkers and common genetic variants with arterial stiffness and wave reflection. *Hypertension*. 2008; 51(6):1651-7.

181. Seals DR, Dinenno FA. Collateral damage: cardiovascular consequences of chronic sympathetic activation with human aging. *Am J Physiol Heart Circ Physiol*. 2004; 287(5):H1895-905.

182. Senitko AN, Charkoudian N, Halliwill JR. Influence of endurance exercise training status and gender on postexercise hypotension. *J Appl Physiol (1985)*. 2002; 92(6):2368-74.

183. Shah PM, Pai RG. Diastolic heart failure. *Curr Probl Cardiol*. 1992; 17(12):786-845.

184. Shek EW, Brands MW, Hall JE. Chronic leptin infusion increases arterial pressure. *Hypertension*. 1998; 31(1 Pt 2):409-14.

185. Shen L, Ma H, Xiang M, Wang J. Meta-analysis of cohort studies of baseline prehypertension and risk of coronary heart disease. *Am J Cardiol*. 2013; 112(2):266-71.

186. Siegel GJ, Agranoff BW, Albers RW, et al. Regulation of Cerebral Metabolic Rate. . 1999.

187. Silventoinen K, Magnusson PK, Neovius M, et al. Does obesity modify the effect of blood pressure on the risk of cardiovascular disease? A population-based cohort study of more than one million Swedish men. *Circulation*. 2008; 118(16):1637-42.

188. Singhal A, Farooqi IS, Cole TJ, et al. Influence of leptin on arterial distensibility: a novel link between obesity and cardiovascular disease? *Circulation*. 2002; 106(15):1919-24.

189. Sobue T, Yokota M, Iwase M, Ishihara H. Influence of left ventricular hypertrophy on left ventricular function during dynamic exercise in the presence or absence of coronary artery disease. *J Am Coll Cardiol*. 1995; 25(1):91-8.

190. Somers VK, Conway J, Coats A, Isea J, Sleight P. Postexercise hypotension is not sustained in normal and hypertensive humans. *Hypertension*. 1991; 18(2):211-5.

191. Sprague AH, Khalil RA. Inflammatory cytokines in vascular dysfunction and vascular disease. *Biochem Pharmacol*. 2009; 78(6):539-52.

192. Stamler J, Stamler R, Neaton JD. Blood pressure, systolic and diastolic, and cardiovascular risks: US population data. *Arch Intern Med*. 1993; 153(5):598-615.

193. Stamler R, Ford CE, Stamler J. Why do lean hypertensives have higher mortality rates than other hypertensives? Findings of the Hypertension Detection and Follow-up Program. *Hypertension*. 1991; 17(4):553-64.

194. Steinberg HO, Chaker H, Leaming R, Johnson A, Brechtel G, Baron AD. Obesity/insulin resistance is associated with endothelial dysfunction. Implications for the syndrome of insulin resistance. *J Clin Invest*. 1996; 97(11):2601-10.

195. Szwajcer A, Tangri N, Arora RC. Non invasive endothelial function testing and risk of adverse outcomes: systematic review literature search protocol. . 2013.

196. Taylor-Tolbert NS, Dengel DR, Brown MD, et al. Ambulatory blood pressure after acute exercise in older men with essential hypertension. *Am J Hypertens*. 2000; 13(1 Pt 1):44-51.

197. Thompson PD, Crouse SF, Goodpaster B, Kelley D, Moyna N, Pescatello L. The acute versus the chronic response to exercise. *Med Sci Sports Exerc*. 2001; 33(6 Suppl):S438,45; discussion S452-3.

198. Tinken TM, Thijssen DH, Black MA, Cable NT, Green DJ. Time course of change in vasodilator function and capacity in response to exercise training in humans. *J Physiol (Lond)*. 2008; 586(20):5003-12.

199. Toda N, Okamura T. Obesity impairs vasodilatation and blood flow increase mediated by endothelial nitric oxide: an overview. *The Journal of Clinical Pharmacology*. 2013; 53(12):1228-39.

200. Tousoulis D, Antoniades C, Stefanadis C. Evaluating endothelial function in humans: a guide to invasive and non-invasive techniques. *Heart*. 2005; 91(4):553-8.

201. Treasure CB, Klein JL, Vita JA, et al. Hypertension and left ventricular hypertrophy are associated with impaired endothelium-mediated relaxation in human coronary resistance vessels. *Circulation*. 1993; 87(1):86-93.

202. Tsukinoki R, Murakami Y, Huxley R, et al. Does body mass index impact on the relationship between systolic blood pressure and cardiovascular disease?: meta-analysis of 419 488 individuals from the Asia pacific cohort studies collaboration. *Stroke*. 2012; 43(6):1478-83.

203. Tuomilehto J. Body mass index and prognosis in elderly hypertensive patients: a report from the European Working Party on High Blood Pressure in the Elderly. *Am J Med*. 1991; 90(3):S34-41.

204. Umemura S, Nyui N, Tamura K, et al. Plasma angiotensinogen concentrations in obese patients. *Am J Hypertens*. 1997; 10(6):629-33.

205. Uretsky S, Messerli FH, Bangalore S, et al. Obesity paradox in patients with hypertension and coronary artery disease. *Am J Med*. 2007; 120(10):863-70.

206. Van Bortel LM, Laurent S, Boutouyrie P, et al. Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *J Hypertens*. 2012; 30(3):445-8.

207. van Trijp MJ, Bos WJ, van der Schouw, Yvonne T, Muller M, Grobbee DE, Bots ML. Non-invasively measured structural and functional arterial characteristics and coronary heart disease risk in middle aged and elderly men. *Atherosclerosis*. 2006; 187(1):110-5.

208. Vanhoutte PM. Endothelial dysfunction the first step toward coronary arteriosclerosis. *Circulation Journal*. 2009; 73(4):595-601.

209. Vasan RS, Beiser A, Seshadri S, et al. Residual lifetime risk for developing hypertension in middle-aged women and men: The Framingham Heart Study. *JAMA*. 2002; 287(8):1003-10.

210. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB. Elevated C-reactive protein levels in overweight and obese adults. *JAMA*. 1999; 282(22):2131-5.

211. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010; 55(13):1318-27.

212. Voetsch B, Jin RC, Loscalzo J. Nitric oxide insufficiency and atherothrombosis. *Histochem Cell Biol*. 2004; 122(4):353-67.

213. Waddell TK, Dart AM, Medley TL, Cameron JD, Kingwell BA. Carotid pressure is a better predictor of coronary artery disease severity than brachial pressure. *Hypertension*. 2001; 38(4):927-31.

214. Wang KL, Cheng HM, Chuang SY, et al. Central or peripheral systolic or pulse pressure: which best relates to target organs and future mortality? *J Hypertens*. 2009; 27(3):461-7.

215. Wang Y, Wang QJ. The prevalence of prehypertension and hypertension among US adults according to the new joint national committee guidelines: new challenges of the old problem. *Arch Intern Med*. 2004; 164(19):2126-34.

216. Wang ZV, Scherer PE. Adiponectin, cardiovascular function, and hypertension. *Hypertension*. 2008; 51(1):8-14.

217. Wassertheil-Smoller S, Fann C, Allman RM, et al. Relation of low body mass to death and stroke in the systolic hypertension in the elderly program. The SHEP Cooperative Research Group. *Arch Intern Med*. 2000; 160(4):494-500.

218. Weber K, Sun Y, Guarda E, et al. Myocardial fibrosis in hypertensive heart disease: an overview of potential regulatory mechanisms. *Eur Heart J*. 1995; 16:24-.

219. Weber KT. The what, why and how of hypertensive heart disease. *J Hum Hypertens*. 1994; 8(9):665-75.

220. Weber MA, Jamerson K, Bakris GL, et al. Effects of body size and hypertension treatments on cardiovascular event rates: subanalysis of the ACCOMPLISH randomised controlled trial. *Lancet*. 2013; 381(9866):537-45.

221. Weber MA, Neutel JM, Smith DH. Contrasting clinical properties and exercise responses in obese and lean hypertensive patients. *J Am Coll Cardiol*. 2001; 37(1):169-74.

222. Weber T, Auer J, O'rourke MF, et al. Increased arterial wave reflections predict severe cardiovascular events in patients undergoing percutaneous coronary interventions. *Eur Heart J*. 2005; 26(24):2657-63.

223. Weisbrod RM, Shiang T, Al Sayah L, et al. Arterial stiffening precedes systolic hypertension in diet-induced obesity. *Hypertension*. 2013; 62(6):1105-10.

224. Weltman A, Weltman JY, Watson Winfield DD, et al. Effects of continuous versus intermittent exercise, obesity, and gender on growth hormone secretion. *J Clin Endocrinol Metab*. 2008; 93(12):4711-20.

225. Wen CP, Cheng TYD, Tsai MK, et al. All-cause mortality attributable to chronic kidney disease: a prospective cohort study based on 462 293 adults in Taiwan. *The Lancet*. 2008; 371(9631):2173-82.

226. Whelton SP, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. *Ann Intern Med*. 2002; 136(7):493-503.

227. Whitworth JA, World Health Organization, International Society of Hypertension Writing Group. 2003 World Health Organization (WHO)/International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens*. 2003; 21(11):1983-92.

228. Whyte LJ, Gill JM, Cathcart AJ. Effect of 2 weeks of sprint interval training on health-related outcomes in sedentary overweight/obese men. *Metab Clin Exp*. 2010; 59(10):1421-8.

229. Williams B, Lacy PS, Thom SM, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation*. 2006; 113(9):1213-25.

230. Wolthuis RA, Froelicher VF, Fischer J, et al. New practical treadmill protocol for clinical use. *Am J Cardiol*. 1977; 39(5):697-700.

231. Woodard C, Quinones M, Alexander J. Pathogenesis of myocardial dysfunction in extreme obesity. In: *Circulation*. AMER HEART ASSOC 7272 GREENVILLE AVENUE, DALLAS, TX 75231-4596; 1978, p. 230-.

232. World Health Organization. Causes of death 2008: data sources and methods. *Geneva: World Health Organization*. 2011.

233. World Health Organization. *Global Health Risks: Mortality and Burden of Disease Attributable to Selected Major Risks*: available at: http://www.who.int/healthinfo/global_burden_disease/global_health_risks/en/; 2009.

234. World Health Organization (WHO. A global brief on hypertension: silent killer, global public health crisis. *Women*. 2015.

235. Yan P, Zhu X, Li H, et al. Association of high blood pressure with renal insufficiency: role of albuminuria, from NHANES, 1999–2006. *PloS one*. 2012; 7(7).

236. Yano Y, Fujimoto S, Sato Y, et al. Association between prehypertension and chronic kidney disease in the Japanese general population. *Kidney Int*. 2012; 81(3):293-9.

237. Yusuf S, Thom T, Abbott RD. Changes in hypertension treatment and in congestive heart failure mortality in the United States. *Hypertension*. 1989; 13(5 Suppl):I74-9.

238. Zeigler ZS, Mullane S, Crespo NC, Buman MP, Gaesser GA. Effects of Standing and Light-Intensity Activity on Ambulatory Blood Pressure. *Med Sci Sports Exerc*. 2015.

239. Zeigler ZS, Swan PD, Bhammar DM, Gaesser GA. Walking Workstation Use Reduces Ambulatory Blood Pressure in Adults With Prehypertension. *J Phys Act Health*. 2015; 12(6 Suppl 1):S119-27.