Resistance Exercise Training Improves Vascular Function after

Acute Exertion in Obese Women

BY

NINA CHERIE FRANKLIN
B.S., University of Illinois at Urbana-Champaign, 2002
M.S., University of Illinois at Chicago, 2006

THESIS

Submitted as partial fulfillment of the requirements
for the degree of Doctor of Philosophy in Kinesiology, Nutrition, and Rehabilitation
in the Graduate College of the
University of Illinois at Chicago, 2012

Chicago, Illinois

Defense Committee:

Dr. Shane A. Phillips, Chair and Advisor
Dr. Charlotte A. Tate, Disability and Human Development
Dr. Timothy J. Koh, Kinesiology and Nutrition
Dr. Krista Varady, Kinesiology and Nutrition
Dr. Mariann Piano, Biobehavioral Health Science

This thesis is dedicated to my husband and very best friend, Woody. Thank you for believing in me and providing me with infinite support throughout this entire process. We still have a long way to go and there is no one I'd rather travel this road with. It is also dedicated to my first-born son, Ramsey. You are my most precious gift. I'm so proud to be your mama. In addition, I'd like to extend thanks to Dr. Charlotte (Toby) Tate, Dr. Sandra Strome, and Dr. Helen Massey for all the helpful advice, funny stories, and never-ending encouragement.

Last, but certainly not least, I'm dedicating this thesis to my mama and daddy. Mama, you're my hero. Through you, I've learned the art of resilience. Thank you for saving my life by doing everything you could to facilitate my dramatic weight loss at the age of 15—a life changing event that made me the woman (and the scientist) I am today. Daddy, thank you for the spiritual guidance that has helped me as a wife, mother, and scientist (in that order). I continue to learn from you.

ACKNOWLEDGEMENTS

First and foremost, I would like to extend my sincerest thanks and appreciation to my committee chairperson, advisor, and friend Dr. Shane A. Phillips for his tireless guidance, unwavering support, and unrelenting patience during this entire process. I also wish to thank the members of my thesis committee—Dr. Charlotte A. Tate, Dr. Timothy J. Koh, Dr. Krista Varady, and Dr. Mariann Piano—for their time, dedication, and direction. Their insight and guidance played a critical role in the development of my research proposal, data analysis, and, ultimately, the successful completion of this project. I will forever be grateful to Dr. Tate who helped me immensely through each phase of my predoctoral research career and taught me the art of leadership. In addition, I would like to graciously thank the NIH, National Heart, Lung, and Blood Institute for financially supporting my project.

I would also like to acknowledge the many individuals who were extremely helpful to me during data collection including: the nursing and administrative staff at the UIC, General Clinical Research Center; the faculty and staff in the Department of Physical Therapy and the Department of Kinesiology and Nutrition; and the Vascular Biology staff in Dr. Phillips' laboratory. I would especially like to thank the professional, graduate, and undergraduate students in the Department of Physical Therapy and the Department of Kinesiology for their invaluable assistance during data collection and analysis for this project. Last, but certainly not least, I must acknowledge the research participants. These individuals deserve more thanks than I can ever give. They were willing to come to the laboratory in rain, sleet, or snow for over 20 visits so that I could collect data. Thank you for making this project easier for me.

TABLE OF CONTENTS

TABLE OF CONTENTS (continued)

LIST OF TABLES

LIST OF FIGURES

LIST OF FIGURES (continued)

LIST OF ABBREVIATIONS

ADI	Adiponectin
AET	Aerobic Exercise Training
ANOVA	Analysis of Variance
BFV	Blood Flow Velocity
BH_4	Tetrahydrobiopterin
BMI	Body Mass Index
BP	Blood Pressure
cGMP	Cyclic Guanosine Monophosphate
CVD	Cardiovascular Disease
ecSOD	Extracellular Superoxide Dismutase
EID	Endothelium-Independent Dilation
ELISA	Enzyme-Linked Immunosorbent Assay
eNOS	Endothelial Nitric Oxide Synthase
FMD	Flow-Mediated Dilation
H_2O_2	Hydrogen Peroxide
HDL	High-Density Lipoproteins
HR	Heart Rate
IL-6	Interleukin-6
IL-10	Interleukin-10
LDL	Low-Density Lipoproteins
LEP	Leptin
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NO	Nitric Oxide

LIST OF ABBREVIATIONS (continued)

OB	Obese
O_2^-	Superoxide
$ONOO^-$	Peroxynitrite
P	Probability
RES	Resistin
RET	Resistance Exercise Training
ROS	Reactive Oxygen Species
RM	Repetition Maximum
sGC	Soluble Guanylate Cyclase
SR	Shear Rate
SWL	Strenuous Weight Lifting
TNF-α	Tumor Necrosis Factor-Alpha
VD	Vascular Dysfunction
VO_2	Functional Capacity
WBC	White Blood Cell

SUMMARY

A study examining the effects of whole-body resistance exercise training on vascular function after acute exertion was carried out in sedentary obese women using a within-subject, repeated measures design. Subjects were evaluated at multiple time points before, during, and after participation in an 8-week moderate-intensity resistance exercise training intervention. At each time point subjects underwent a single bout of strenuous weight lifting designed to increase blood pressure. Vascular function was assessed before and after strenuous weight lifting using brachial artery flow-mediated dilation and blood samples were obtained for measurement of circulating adipokine and cytokine levels. Other relevant physical and physiological variables assessed included: fasting lipids and glucose, red and white blood cells, platelets, hemoglobin, and hematocrit, blood pressure, heart rate, anthropometrics, body composition, daily physical activity, functional capacity, muscular strength, and dietary patterns.

Brachial artery flow-mediated dilation was impaired in sedentary obese women after a single bout of strenuous weight lifting and an 8-week moderate-intensity resistance exercise training intervention completely reversed this impairment. In addition, resistance exercise training resulted in improvements in waist circumference, body composition, functional capacity, and muscular strength. There were no significant changes in fasting lipids or glucose levels, red or white blood cells, platelets, hemoglobin, or hematocrit, blood pressure, or heart rate as a result of the resistance exercise training intervention. Changes in brachial artery flow-mediated dilation post-acute exertion and after 8 weeks of resistance exercise training were not linked to obesity-related changes in circulating adipokine and cytokine levels.

I. RESEARCH PROBLEM

A. Introduction to the Problem

Sedentary lifestyle is a significant health problem in the United States (US) in that over 60 percent of adults do not achieve the minimum recommended amount of daily physical activity and 25 percent are not physically active at all in their leisure time (1). Low levels of physical activity promote obesity and contribute to other chronic diseases, such as hypertension, type 2 diabetes mellitus, and some forms of cancer (2,3). Furthermore, sedentary lifestyle and obesity are independent risk factors for atherosclerotic cardiovascular disease (CVD) (2,4). Vascular dysfunction (VD) is a key event in the development of atherosclerosis (5,6) and associated with a sedentary lifestyle in otherwise healthy adults (7-9). In addition, VD may be exacerbated in sedentary adults who are obese since increased body fat is associated with elevated levels of pro-atherogenic inflammatory adipokines that reduce nitric oxide (NO) bioavailability in vascular endothelial cells by elevating the production of reactive oxygen species (ROS) (10-12). Since VD is a precursor of CVD (6) and associated with a sedentary lifestyle (9), understanding the mechanisms by which physical activity improves vascular function is of clinical importance.

Regular physical activity, in the form of aerobic and resistance exercise training, has beneficial effects on CVD and risk factors (13-15). Aerobic exercise training (AET) reduces total body fat and improves overall vascular function (16-18). During acute aerobic exercise, blood flow increases continuously under moderate pressures eliciting prolonged endothelial shear stress that stimulates the production and release of NO which promotes arterial vasodilation and facilitates blood flow (19-21). Resistance exercise training (RET) moderately reduces body fat (22-24) while preserving fat-free mass (22,25) and is also associated with

favorable effects on vascular function (26), however, the precise mechanisms underlying these positive effects are not completely understood. On the one hand, acute resistance exercise increases blood flow intermittently and while under relatively elevated pressures, likely yields increased shear stress and improved NO-mediated arterial vasodilation (27,28). On the other hand, it is debatable whether or not elevations in blood pressure (BP) during acute resistance exercise counteract the benefits of regular RET since an excessively high elevation in BP during acute exertion can induce VD and increase ROS generation (28,29).

Research in our laboratory suggests that regular RET protects against VD in response to acute exertion. We have shown that brachial artery flow-mediated dilation (FMD), a measure of vascular function, is significantly impaired in healthy sedentary lean adults compared to resistance-trained adults following a single bout of strenuous weight lifting (SWL) despite similar elevations in BP (29). Furthermore, microvessels obtained from subcutaneous gluteal fat biopsy specimens of sedentary lean adults demonstrate impairment of vascular function and increased superoxide (O_2^-) fluorescence after SWL compared to resistance-trained adults implicating the role of increased ROS generation in VD. However, it is unknown whether or not sedentary obese adults are more susceptible to impaired vascular function after acute exertion. Several studies have demonstrated impairment of vascular function in overweight and obese adults (30) and modest improvements following regular RET (12,31), but such studies are limited and changes in FMD have not been evaluated immediately after acute exertion which is known to induce VD. RET has also been shown to lower markers of exertion-induced oxidative stress (31,32) and elicit improvements in antioxidant statuses of overweight and obese adults (12) suggesting that the beneficial effects of resistance exercise on vascular function in this population may be a consequence of reduced ROS production and enhanced NO bioavailability.

Excess body fat is associated with a pro-atherogenic milieu involving increased secretion of the inflammatory adipokines leptin (LEP) and resistin (RES) and decreased secretion of the anti-atherogenic adipokine adiponectin (ADI) (29). Leptin and RES have been shown to increase production of pro-inflammatory cytokines (i.e. tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6)) in leukocytes (29,33), and induce ROS production in vascular endothelial cells which may play a role in directly inactivating NO (12,31). In contrast, ADI has been demonstrated to enhance the production of anti-inflammatory cytokines (i.e. interleukin-10 (IL-10)) (33,34), increase vascular endothelial NO production (35), and suppress ROS generation (36), all of which protect against VD. These data, taken together with research from our laboratory, indicates that regular RET in the presence of obesity may protect against acute exertion-induced impairment of vascular function by beneficially altering adipokine and cytokine profiles.

B. Purpose of the Study

The long-range goal of this research is to understand the mechanisms whereby exercise training protects the vascular endothelium and prevents CVD. The major purpose of this study was to determine if regular RET improves vascular responses to acute exertion during a single bout of SWL in sedentary obese adults. We also examined whether or not there were any changes in circulating adipokine and cytokine levels in sedentary OB adults as a result of RET. The central hypothesis was that RET would protect against acute exertion-induced impairment of vascular function in sedentary OB adults by decreasing circulating levels of LEP, RES, TNF-α, and IL-6, and increasing circulating levels of ADI and IL-10. This central hypothesis was tested by the following specific aims:

1. To examine the effects of acute exertion on vascular function and circulating adipokine and cytokine levels in sedentary obese adults.
2. To determine if an 8-week resistance exercise training intervention improves vascular responses to acute exertion in sedentary obese adults.

For the first specific aim, the hypothesis was that acute exertion would impair vascular function in sedentary OB adults and this impairment would be associated with increased circulating levels of LEP, RES, TNF-α, and IL-6, and reduced circulating levels of ADI and IL-10. The hypothesis for the second specific aim was that 8 weeks of RET would protect against acute exertion-induced impairment of vascular function and changes in circulating adipokine and cytokine levels would be involved in the improved vascular response.

C. Rationale and Significance of the Study

The rationale for investigating the effects of a single bout of SWL on vascular function in sedentary OB adults stemmed from research in our laboratory that demonstrates impaired vascular function and enhanced ROS generation in sedentary lean adults after such acute exertion. Sedentary adults who are also obese may express elevated concentrations of pro-atherogenic inflammatory adipokines and cytokines and, therefore, exhibit augmented VD following acute exertion. Since exercise training has been shown to induce significant benefits in individuals with antecedent VD, sedentary OB adults may be more amendable to an intervention.

We chose to examine the effects of resistance exercise in sedentary OB adults because this type of exertion introduces an alternative type of shear stress to the vascular endothelium (i.e. intermittent blood flow under relatively elevated pressures) and does not significantly reduce body fat. As such, implementing a RET intervention permits an investigation of the isolated

effects of exercise-related shear stress on vascular function in individuals who are obese. Since very little is known about the vascular effects of resistance exercise, understanding how RET may protect against acute exertion-induced VD in the presence of obesity may yield novel candidates for therapeutic strategies aimed at preventing and treating CVD.

II. LITERATURE REVIEW

A. Introduction to the Literature

Three areas of research are relevant to the literature presented in this review: sedentary lifestyle, adult obesity, and VD. These topics are discussed in detail as they relate to atherosclerotic CVD when relevant. Within the context of this review, key links between sedentary lifestyle, adult obesity, and VD are highlighted as they pertain to the research study. Sedentary lifestyle and obesity are independent risk factors for CVD and contribute to other major risk factors including hypercholesterolemia, hypertension, and type 2 diabetes mellitus (2-4). Furthermore, sedentary lifestyle and obesity are linked to VD which irrefutably contributes to atherogenesis (37,38). Vascular dysfunction is proposed to represent a pathophysiologic mechanism linking sedentary lifestyle and obesity to CVD risk, however, the precise mechanism by which this occurs is still under debate.

B. Vascular Function

Broadly speaking, vascular function refers to a variety of physiologic processes related to maintenance of vascular wall homeostasis, namely the functional integrity of the endothelium. The endothelium is composed of a monolayer of endothelial cells that form the inner lining of the vasculature and is, therefore, strategically located between the circulating blood and vascular smooth muscle cells. Once thought of as merely a physical barrier separating circulating blood from surrounding tissues, the endothelium is now regarded as a complex structure that plays a critical role in regulating vascular wall homeostasis. Under normal physiologic conditions, the endothelium modulates vascular smooth muscle tone by secreting a variety of bioactive molecules that promote vasodilation and vasoconstriction (39); prevents atherosclerosis through

its anti-proliferative and anticoagulant effects on the vascular wall (40,41); controls inflammation by preventing leukocyte activation and adhesion (39); and maintains oxidative-anti-oxidative balance within the vasculature (40).

In pioneering experiments, Furchgott and Zawadzki discovered that an endothelium-derived relaxing factor played a fundamental role in regulating vascular function (42) and Ignarro and colleagues (43) later identified this factor as NO. Since these earlier experiments, a number of additional endothelium-derived vasodilators (i.e. prostacyclin and endothelium-derived hyperpolarizing factor) and vasoconstrictors (i.e. endothelin-1, angiotensin II, thromboxane A2) have been uncovered (22,44). However, NO is still reported to be the chief regulator of vascular function playing a critical role in endothelium-dependent vasodilation (22). Endothelium-derived NO is formed from the guanidine-nitrogen terminal of L-arginine through the action of the enzyme endothelial nitric oxide synthase (eNOS) (also known as nitric oxide synthase 3 or constitutive nitric oxide synthase) upon activation by receptor-dependent agonists (i.e. acetylcholine) or receptor-independent stimuli (i.e. shear stress) (39). In the context of blood flow-induced shear stress, elevated cytosolic calcium (Ca^{2+}) triggers activation of eNOS to catalyze the conversion of L-arginine to L-citrulline and NO, with tetrahydrobioterin (BH_4) and nicotinamide adenine dinucleotide phosphate (NADPH) as essential cofactors (37,45). Once NO is released from the endothelium, it diffuses through the vascular wall and into adjacent smooth muscle cells, where it signals the soluble enzyme guanylate cyclase (sGC) to produce cyclic guanosine monophosphate (cGMP), the second messenger of NO (39). This signaling cascade ultimately causes smooth muscle cells to relax which results in vasodilation (Figure 1). Physiologic impairment of endothelium-dependent vasodilation can lead to deleterious alterations in blood flow during physiologic stress (i.e. exercise, hypoxia, hemorrhage) and

contribute to elevations in blood pressure promoting the development of atherosclerotic CVD (30,38,46).

C. Vascular Dysfunction

Vascular dysfunction is a pathological condition during which the physiologic activity of the endothelium is impaired. This condition most commonly results from an imbalance between vasodilator and vasoconstrictor substances produced by the endothelium and there is ample evidence demonstrating that the most prominent feature of VD is a reduction in endothelium-derived NO bioavailability (40,47). Although the exact mechanism by which this reduction in NO bioavailability occurs is still under debate, several key mechanisms have been put forward including: disturbances in the NO signaling pathway; reduced bioavailability of L-arginine and/or BH_4; modified expression and functional activity of eNOS; extracellular scavenging of NO by reactive oxygen species (ROS); and increased production of endothelium-derived vasoconstrictors.

The presence of VD has been demonstrated in a variety of chronic diseases, including hypertension, type II diabetes mellitus, renal disease, and obesity (2,3). Its pathophysiology in these disease states is linked to both oxidative stress and an overexpression of pro-inflammatory mediators (i.e. TNF-α and IL-6). Oxidative stress can result from increased ROS production, impairment of antioxidant defenses, or both (Figure 2). Reactive oxygen species are natural by-products of cellular metabolism. At normal physiologic levels, ROS have an important role in cellular signaling; however, when produced in excess, they can have detrimental effects on cell function. In the vascular wall, production of ROS such as superoxide (O_2^-) occurs when the enzyme NADPH oxidase transfers reducing equivalents from intracellular NADPH across the endothelial cell membrane to couple with molecular oxygen (48,49). Once the coupling occurs,

NADPH oxidase-derived O_2^- is capable of mediating oxidative stress and VD by reducing NO bioavailability. Nitric oxide can react with O_2^- to produce an extremely potent oxidant called peroxynitrite ($ONOO^-$) (36,49). In a healthy vascular wall, the antioxidant catalytic activity of the extracellular enzyme superoxide dismutase (ecSOD) can lead to rapid dismutation of O_2^- to less potent molecules of hydrogen peroxide (H_2O_2) and oxygen (36,50). However, in the presence of inflammatory-driven chronic disease states where ROS generation is augmented, excess O_2^- can react with NO generated by endothelial cells to form $ONOO^-$ (10,37,44). If O_2^- production overwhelms the antioxidant capacity of endothelial cells the result is oxidative stress. Moreover, $ONOO^-$ inhibits eNOS production and changes the mission of eNOS from synthesis of NO to synthesis of ROS which further enhances oxidative stress and VD (36,49,50).

D. Obesity and Vascular Dysfunction

Obesity is defined as an abnormal accumulation of adipose tissue and is typically determined by the body mass index (BMI) which is calculated as weight (in kilograms) divided by the square of the height (in meters) (51). According to guidelines established by the National Institutes of Health (NIH), adults with a BMI between 25.0 and 29.9 are considered overweight, while those with a BMI of 30.0 or greater are classified as obese (52). Rates of overweight and obesity among adults in the US have doubled over the last few decades. Currently, 2 in 3 adults are overweight or obese which constitutes over 150 million adults (51,52). Overweight and obesity rates have also increased on a global scale. According to the World Health Organization (WHO), there are nearly 1.6 billion overweight adults and over 400 million of them are obese (53).

Current findings suggest that excess adipose tissue, especially in the visceral region, propagates an inflammatory response characterized by leukocyte infiltration (i.e. neutrophils,

monocytes/macrophages, T-cells) (12,54,55) and increased secretion of adipose tissue-derived pro-inflammatory adipokines (i.e. LEP and RES) (56,57) and well-established inflammatory mediators (i.e. TNF-α and IL-6) (30,58). In addition, production of anti-inflammatory adipokines and cytokines (i.e. ADI and IL-10) is reduced in the presence of excess adipose tissue which exacerbates the obesity-induced inflammatory response (56,59).

The pro-inflammatory milieu associated with excess adipose tissue may directly impact vascular function (12,60,61). During obesity, inflammatory cytokines such as TNF-α and IL-6 act on leukocytes and endothelial cells producing ROS and inducing oxidative stress and, consequently, VD. In addition, a growing body of evidence suggests that the adipokines LEP and RES play major roles in obesity-related VD by inducing oxidative stress and vascular inflammation through local and systemic pathways (62-64). In contrast, ADI and IL-10 are suggested to preserve vascular function by enhancing production of NO, attenuating ROS production, and protecting endothelial cells from inflammatory processes that result from exposure to other adipokines and cytokines (65-67). Obesity has also been shown to augment oxidative stress in response to acute exertion (68). The following data summarizes effects of both pro- and anti-inflammatory adipokines and cytokines on vascular function in obesity.

1. <u>Pro-Inflammatory Adipokines and Cytokines</u>

The pathogenesis of obesity-induced VD is linked to increases in pro-inflammatory adipokines and cytokines including LEP, RES, TNF-α, and IL-6. Leptin mediates VD through mechanisms that facilitate oxidative stress limiting the bioavailability of NO. In small coronary arteries of viscerally obese pigs with hyperleptinemia, agonist-induced endothelium-dependent vasodilation is impaired while vascular O_2^- levels are increased due to enhanced expression of NADPH-oxidase. Pigs with hyperleptinemia also exhibit increased rates of tyrosine nitration,

which is mediated by $ONOO^-$, confirming that LEP induces oxidative stress through O_2^- scavenging of NO and formation of $ONOO^-$ (69). In addition, eNOS expression is enhanced while intracellular L-arginine levels and NO production are reduced in aortic endothelial cells of obese mice with hyperleptinemia, suggesting that eNOS activity is modified in the presence of increased LEP. As a precursor to NO production, L-arginine oxidation is coupled to the enzymatic reduction of O_2^- by eNOS, therefore, low levels of L-arginine can result in uncoupling of eNOS which leads to enhanced generation of O_2^- as opposed to NO. Indeed, O_2^- and $ONOO^-$ $ONOO^-$ generation are increased in hyperleptinemia (69,70) suggesting that increased LEP levels in obesity promote uncoupling of eNOS due to reduced intracellular L-arginine resulting in oxidative stress and, consequently, reduced NO bioavailability (70). In humans, LEP enhances c-reactive protein (CRP) expression in coronary artery endothelial cells through increased ROS production (71). In addition, LEP augments expression of eNOS in cultured endothelial cells after agonist-mediated stimulation and increases O_2^- and $ONOO^-$ levels leading to reductions in NO bioavailability which may be linked to $ONOO^-$-induced eNOS uncoupling facilitating an environment of oxidative stress (70).

In contrast to LEP, the physiologic role of RES in the pathophysiology of obesity remains controversial, however, evidence suggests that this adipokine directly mediates pro-inflammatory activation of endothelial cells and VD (29,72). Endothelial cells in culture respond to RES treatment by enhancing endothelin-1 (ET-1) production and expression which can impair vascular function (73). Resistin also augments expression of vascular cell adhesion molecule-1 (VCAM-1) and the chemokine monocyte-chemotactic protein-1 (MCP-1), which can trigger recruitment of monocytes/macrophages to endothelial and adipose tissue cells, enhance oxidative stress, and contribute to VD (73). As evidence, RES has been demonstrated to downregulate

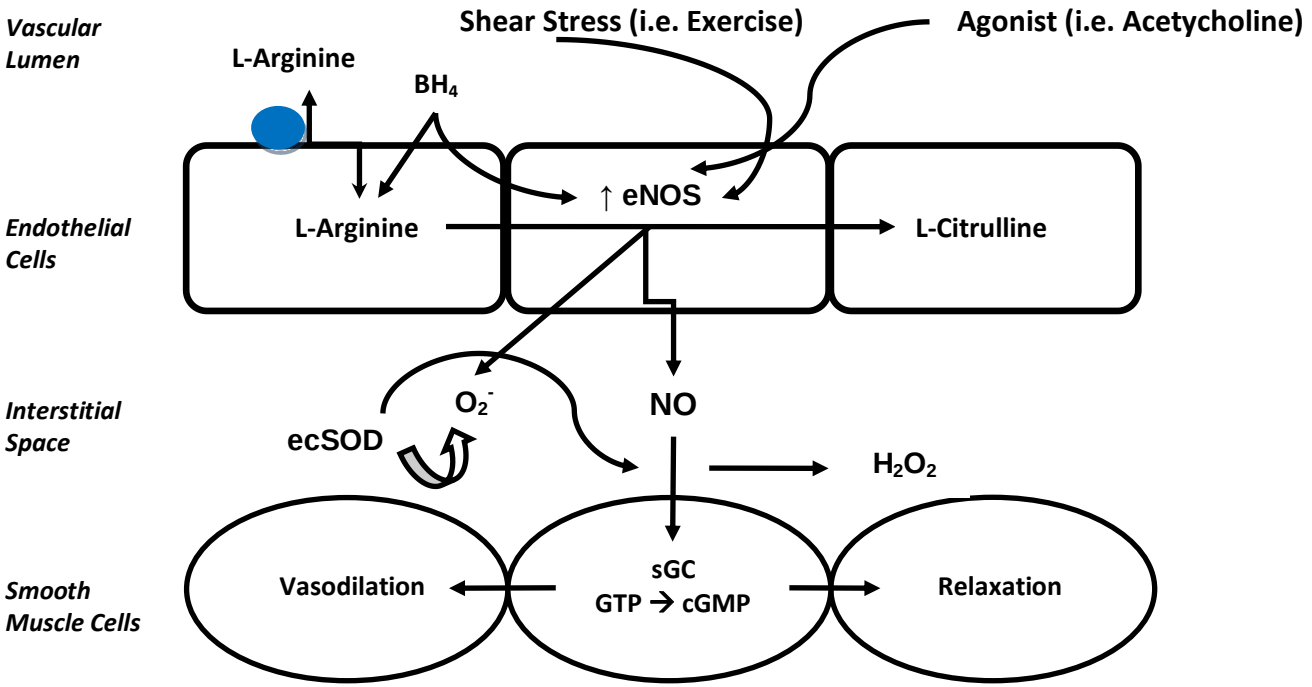


Figure 1. Nitric oxide (NO)-mediated endothelium-dependent vasodilation. In response to shear stress or agonist stimulation, NO is produced by endothelial nitric oxide synthase (eNOS) from L-Arginine with tetrahydrobioterin (BH_4) acting as an essential cofactor. Production of superoxide (O_2^-) occurs as a by-product of NO synthesis, but the antioxidant activity of extracellular superoxide dismutase (ecSOD) leads to rapid dismutation of O_2^- to less potent molecules of hydrogen peroxide (H_2O_2) and oxygen in order to inhibit NO scavenging. Subsequently, NO diffuses into adjacent smooth muscle cells, where it signals the soluble enzyme guanylate cyclase (sGC) to produce cyclic guanosine monophosphate (cGMP), the second messenger. This signaling cascade ultimately causes smooth muscle cells to relax which results in vasodilation.

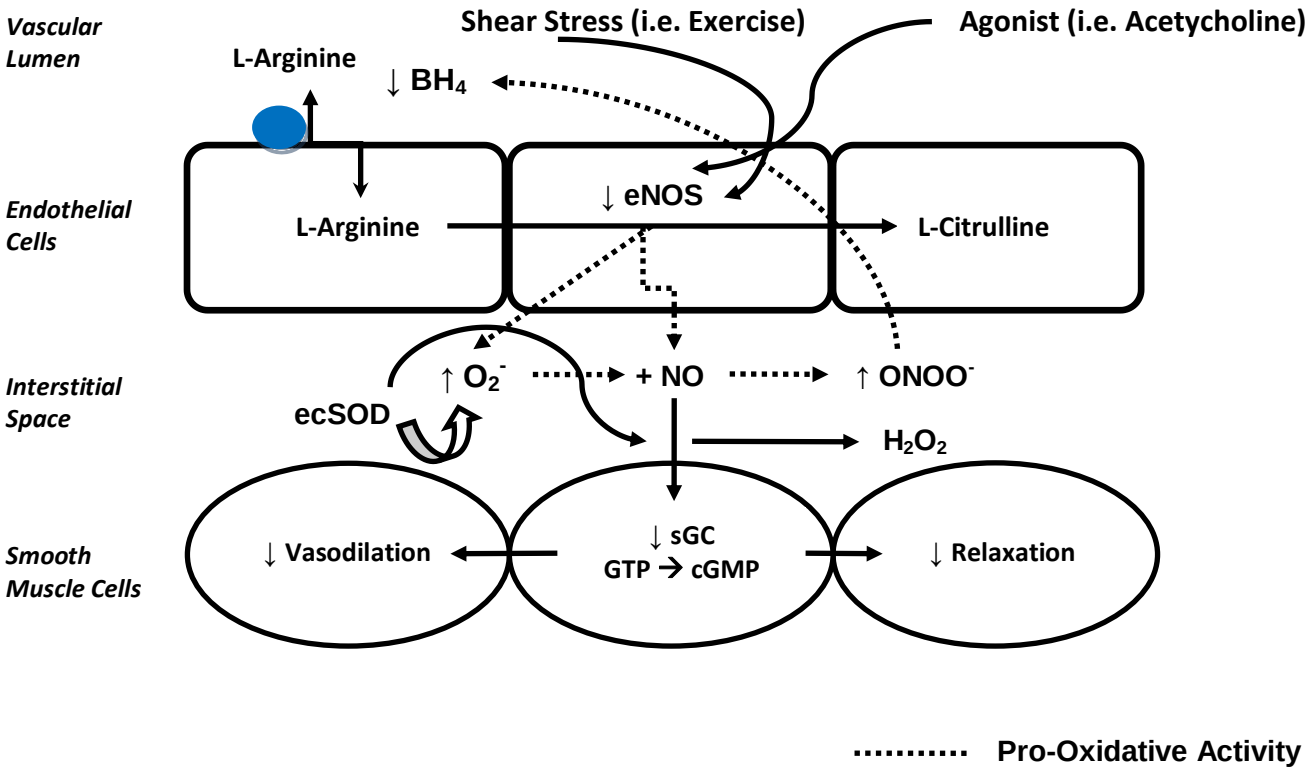


Figure 2. Interactions between nitric oxide (NO) and reactive oxygen species (ROS). The ROS superoxide (O_2^-) mediates oxidative stress and vascular dysfunction (VD) by reducing NO bioavailability. Excess generation of O_2^- overwhelms the antioxidant capacity of vascular cells which can lead to increased scavenging of NO and production of the potent oxidant peroxynitrite ($ONOO^-$), creating a state of oxidative stress. Increased OONO- can further decrease NO bioavailability by reducing the function of tetrahydrobiopterin (BH_4), a critical cofactor for eNOS. Reduced BH_4 changes the mission of eNOS from NO production to biosynthesis of ROS which further enhances oxidative stress. Collectively these interactions between NO and ROS can lead to reduced stimulation of soluble guanylate cyclase (sGC) signaling, and consequently, impaired vasodilation.

eNOS expression, augment O_2^- production, and reduce endothelium-dependent vasodilation in porcine coronary arteries (74). Resistin also promotes human vascular smooth muscle cell proliferation which contributes to atherosclerosis (75) as evidenced by elevated levels of circulating RES in the presence of premature coronary artery disease (76).

The cytokine TNF-α is a crucial mediator of inflammation that is produced by monocytes, lymphocytes, adipose tissue, and muscle (77). This cytokine increases expression of adhesion molecules on endothelial and vascular smooth muscles cells through activation of nuclear factor κB (NF-κ B) which promotes systemic inflammation as well as VD. In small arteries from visceral fat of obese patients, TNF-α production and inducible nitric oxide synthase (iNOS) expression are increased (78). Expression of iNOS is most common in a highly oxidative environment, in which NO reacts with O_2^- leading to OONO- formation and, consequently, an iNOS-induced uncoupling of eNOS (79). Indeed, TNF-α has been shown to contribute to a reduction in NO bioavailability by promoting O_2^- generation through NADPH oxidase in obesity (80).

Interleukin-6 is another pro-inflammatory cytokine that exerts many effects that mediate VD in obesity including increased ROS generation and decreased production of NO (81). The interaction between IL-6 and other pro-inflammatory adipokines is complex. For example, the production of IL-6 along with TNF-α is stimulated by both LEP and RES. Leptin promotes proliferation and activation of monocytes through increases in IL-6 and TNF-α (55,82). In addition, RES enhances the expression and production of IL-6 in human adipose tissue (83) and promotes inflammation by enhancing expression of both IL-6 and TNF-α in cultured macrophages. Resistin also activates mouse and human macrophages and stimulates their secretion of TNF-α and other interleukins (84).

2. Anti-Inflammatory Adipokines and Cytokines

Obesity, especially visceral obesity, is associated with reduced levels of anti-inflammatory adipokines and cytokines including ADI and IL-10. In contrast to the pro-inflammatory adipokines LEP and RES, vascular function is preserved by ADI through anti-atherogenic mechanisms that contribute to enhancement of NO bioavailability. Increased leukocyte adhesion and decreased NO bioavailability have been exhibited in adiponectin knock-out mice (85). In addition, adiponectin deficiency is associated with increased tyrosine nitration, NADPH oxidase expression, and vascular O_2^- production (86,87), all of which are consistent with increased NO scavenging and enhanced $ONOO^-$ production. Furthermore, neutrophil O_2^- generation is inhibited by ADI through regulation of the NADPH-oxidase pathway in humans (54).

There are many studies that show direct links between hypoadiponectemia, obesity, and VD. Endothelium-dependent vasodilation is reduced in aortas of adiponectin knock-out mice with high fat diet-induced obesity (88). Impaired endothelium-dependent vasodilation is also exhibited in aortas of diet-induced obese rats and attenuated in the presence of ADI (89). In addition, microvascular function is impaired in obese humans with low levels of circulating ADI (90).

Similar to ADI, the anti-inflammatory cytokine IL-10 inhibits biosynthesis of pro-inflammatory cytokines and prevents VD by enhancing NO bioavailability. It exerts its effects primarily through down-regulation of ROS production by leukocytes (91,92). In mice, IL-10 prevents impairment of endothelium-dependent vasodilation caused by TNF-α by preserving eNOS expression in aortic rings (93). In addition, IL-10 suppresses TNF-α-induced oxidative stress in cardiac muscle cells (94) and protects carotid arteries against VD during acute

inflammation by limiting O_2^- generation (95). Interleukin-10 levels are reduced in obesity and independently related to low levels of ADI (96).

Taken together, the presented data suggests that pro- and anti-inflammatory adipokines and cytokines have diverse effects on vascular function. Furthermore, adverse alterations in production of these adipokines and cytokines in the obese state may augment VD due to increased ROS production that reduces NO bioavailability. Therefore, this research tested the hypothesis that obese adults exhibit augmented VD associated with increased circulating levels of LEP, RES, TNF-α, and IL-6, and reduced circulating levels of ADI and IL-10.

E. Sedentary Lifestyle and Vascular Dysfunction

Sedentary lifestyle is a term used to describe individuals who do not engage in regular exercise training or those who do not meet the minimum physical activity recommendations for health benefits (97). The US Surgeon General recommends inclusion of at least 30 minutes of moderate physical activity on most, if not all, days of the week for significant health benefits to be achieved (98). More specific exercise guidelines published by the American College of Sports Medicine (ACSM) and the American Heart Association (AHA) recommend participation in 20 to 30 minutes of moderate- to vigorous-intensity AET, three to five days per week with inclusion of at least two days of RET (97). Globally, sedentary lifestyle is a leading cause of preventable death and a major independent risk factor across a broad spectrum of chronic diseases including CVD, hypertension, type 2 diabetes mellitus, and some forms of cancer (99). Despite the known risks more than 60% of adults in the US do not engage in recommended amounts of physical activity and of that, 25% are completely inactive during their leisure time (97,98).

Low levels of physical activity and sedentary behaviors contribute to obesity which enhances the risk of chronic health problems (97,98). Epidemiological studies provide evidence suggesting that individuals who regularly engage in sedentary behaviors are more likely to be overweight or obese than those who are regularly physically active (97,100). Paradoxically, physical activity has been shown to provide a protective effect against health risks associated with obesity, conferring health benefits independent of changes in body weight or composition (101,102), which suggests that overweight and obese individuals can obtain the same benefits of physical activity as normal weight individuals. For example, studies examining associations between physical activity and BMI as risk factors for hypertension and type 2 diabetes mellitus show that overweight and obese individuals who are regularly physically active have lower morbidity and mortality rates than normal weight individuals who are sedentary (103,104). Furthermore, physical activity in the form of exercise training has been shown to beneficially alter lipid levels and dramatically improve vascular function in overweight and obese adults (17,105,106).

A sedentary lifestyle has been shown to induce VD by enhancing ROS production and decreasing NO bioavailability (7,107). Since blood flow-related shear stress is a major stimulus to NO release from the endothelium, disturbed flow or low shear stress is the likely mechanism by which endothelial cell function is altered with a sedentary lifestyle. Physical activity in the form of exercise dramatically increases shear stress and is, therefore, a potent stimulus for NO production. Evidence suggests that AET enhances NO bioavailability and reduces oxidative stress through upregulation of eNOS and ecSOD expression in resistance vessels (22,108). In addition, various forms of AET have been shown to improve endothelium-dependent FMD, a marker of vascular function, in conduit arteries (108). Comparably, RET has been shown to

improve endothelium-dependent FMD (106) and may protect against VD through regulation of eNOS (109) and reduction of oxidative stress (110); however, the specific mechanism by which vascular function is protected is unknown. It is also important to note that impaired vascular function is more capable of augmentation by exercise training than well-preserved function in healthy individuals (22) as evidenced by training studies in subjects with excess adiposity (106), chronic heart failure (111), and type 2 diabetes mellitus (112), all of whom exhibit VD. A summary of data relating AET and RET to vascular function follows.

1. <u>Aerobic Exercise Training</u>

Aerobic exercise training improves endothelium-dependent vasodilation in both animal models and humans through mechanisms that enhance NO bioavailability. Five to nine weeks of moderate-intensity AET enhances endothelium-dependent vasodilation and eNOS expression in previously physically inactive young mice (7). In addition, low- and moderate-intensities of AET improve endothelium-dependent vasodilation and NO bioavailability in aortas of obese, diabetic mice independent of changes in hyperglycemic status through upregulation of eNOS and specific SOD isoforms resulting in reduced NO-dependent oxidative stress (112,113). Moderate-intensity AET also has an added benefit of lowering body weight in obese, diabetic mice (113). In the context of adipokines, AET decreases circulating levels of LEP in obese rats (114). Aerobic exercise training also suppresses inflammation and oxidative stress in aortas of diabetic mice due to improvements in ADI (93).

In humans, AET has been shown to reduce circulating levels of LEP and RES (115,116), increase circulating levels of ADI (117), and enhance expression of ADI receptors in adipose tissue as well as skeletal muscle (118). Aerobic exercise training also improves vascular function through enhanced NO-mediated, endothelium-dependent vasodilation and increased

antioxidant capacity. Some research suggests that AET corrects VD through local repetitive increases in shear stress on the endothelium of trained extremities. As evidence, three months of lower-limb dominant AET using cycle ergometry enhanced FMD in the posterior tibial arteries of patients with chronic heart failure while brachial artery FMD was not affected (119) suggesting that the training effects of AET on vascular function are localized as opposed to systemic. Similarly, 10 weeks of participating in moderate-intensity lower-limb dominant AET led to significant improvements in posterior tibial artery FMD but not brachial artery FMD in patients with coronary artery disease (CAD) (109). In other studies, exercise-induced vasodilation in the forearm was associated with increased forearm circulating levels of NO biomarkers in the exercised arm but not in the non-exercised arm (109). Taken together, these findings suggest that the beneficial effects of AET in humans may be more pronounced in the circulation of exercising limbs.

2. <u>Resistance Exercise Training</u>

Although specific effects of exclusive RET on vascular function have received less attention than those of AET, research indicates that this form of exercise protects against VD in both animal models and human subjects through mechanisms that enhance NO production and promote vascular remodeling induced by shear stress. In a recent study, six weeks of RET was shown to attenuate age-associated VD in femoral arteries of rats and increased heat shock protein 90 expression which is a known regulator of eNOS activity and coupling (109). Since coupling of eNOS is associated with enhanced generation of NO these data indicate that the improved endothelium-dependent vasodilation after RET is mediated by the re-coupling of eNOS and the generation of NO.

In humans, RET appears to induce the physiologic shear stress necessary for NO generation. Six weeks of moderate-intensity RET reduced central BP and enhanced microvascular function as assessed by strain gauge plethysmography before and during reactive hyperemia in healthy young sedentary males (23). Furthermore, in a comparative study of various forms of exercise training, 4 months of moderate-intensity RET alone or high-intensity RET with AET led to significant increases in forearm blood flow as measured by strain gauge plethysmography during reactive hyperemia compared to high-intensity RET alone (120). In studies of brachial artery vasodilation, 12 months of moderate-intensity RET led to significant improvements in FMD among healthy overweight women (106) while 12 weeks of RET improved FMD and increased brachial artery diameter, a marker of vascular remodeling. This evidence suggests that moderate-intensity RET can independently enhance vascular function.

Blood pressure is significantly elevated during resistance exercise. As such, it is currently debatable whether or not elevations in BP during a single bout of resistance exercise counteract the benefits of regular RET since an excessively high elevation in BP during acute exertion can induce heightened oxidative stress and VD in sedentary individuals (26,121). However, research suggests that regular RET does not exacerbate resting or exercise BPs and may have beneficial effects. Six months of RET with heavy loads has been shown to normalize resting BP in older adults with hypertension (122) while just 9 weeks of dynamic RET reduces diastolic BP (123).

Regular whole-body RET has been shown to protect against oxidative stress induced by acute exertion (32). In addition, recent findings from our laboratory suggest that RET protects against VD and that this effect may be related to changes in adipokine profiles in healthy subjects (124). After undergoing a single bout of SWL, FMD is significantly impaired in

sedentary adults compared to resistance-trained adults. Furthermore, among resistance-trained individuals, improvements in FMD were associated with increased ADI and decreased RES suggesting that regular RET may alter adipokine profiles in a manner that protects against VD. These findings suggest that RET among obese individuals may improve vascular function by reducing pro-atherogenic adipokines known to stimulate ROS in the endothelium. Therefore, this research tested the hypothesis that regular RET protects against impairment of vascular function after SWL and that changes in circulating adipokine and cytokine profiles are involved in the improved vascular response.

F. Summary

A sedentary lifestyle appears to effect vascular function through impairment of NO production in the endothelium primarily as a result of insufficient exposure to physiologic shear stress (22,24). These effects may be amplified in the presence of obesity, especially during acute exertion which is known to induce VD. Furthermore, adverse alterations in production of pro- and anti-inflammatory adipokines and cytokines in the obese state may augment VD due to deleterious effects on NO bioavailability (Figure 3). As previously noted, impaired vascular function may be more amendable to an exercise intervention and RET appears to attenuate VD through mechanisms that beneficially modulate adipokine and cytokine profiles. Therefore, sedentary individuals who are obese may likely experience improvements in NO bioavailability and vascular function after regular RET (Figure 4).

G. Pilot Study

Current research in our laboratory focuses on studying the effects of various conditions and lifestyles on vascular function as well as evaluating treatments to improve VD. Prior to

initiating this pilot study, we had strong feasibility data showing that we could measure NO-mediated endothelium-dependent vasodilation of the brachial artery using FMD technique in similar age subjects. Flow-mediated dilation is a widely accepted, non-invasive method during which high-resolution ultrasound is used to evaluate reactivity in peripheral vascular beds at rest, during reactive hyperemia produced by a brief blood flow occlusion, and during endothelium-independent dilation (EID) induced by nitroglycerin (NTG) stimulation of sGC. Using techniques pioneered by Celermajer and colleagues (5), we have performed nearly 200 FMD studies with low inter-observer variability and vascular responses consistent with those reported by others (125,126).

1. Introduction

Previous studies in our laboratory have shown that a single bout of SWL impairs brachial artery FMD in sedentary lean adults compared to resistance-trained adults despite similar elevations in BP. However, the effects of SWL in obese adults had not been demonstrated; therefore, it was unknown whether or not obese individuals were more susceptible to impaired vascular function after acute resistance exercise. As such, the purpose of this pilot study was to examine whether a single bout of SWL would impair brachial artery FMD in sedentary but otherwise healthy obese adults. In addition, we sought to determine if changes in FMD associated with SWL were more severe in sedentary obese adults compared to sedentary lean adults.

2. Methods

Seventeen healthy young women were studied. Inclusion criteria were as follows: 18 to 40 years of age, obese (OB) (BMI 30.0-40.0 kg/m^2) or lean (LN) (BMI 18.5-24.9 kg/m^2), sedentary (less than 150 minutes of moderate physical activity/week), no history of CVD,

hypertension, hypercholesterolemia, diabetes mellitus or thyroid dysfunction, not currently or recently pregnant or lactating, no history of cancer, no history of smoking (for at least 6 months prior to participation), no history of amenorrhea or irregular menses, and no use of vasoactive medications. Written informed consent was obtained from all subjects prior to participation. The study protocol was approved by the Office for the Protection of Research Subjects and the Institutional Review Board (IRB) of the University of Illinois at Chicago (UIC).

All measurements were performed after a 12-hour overnight fast. Lipid panels and glucose measurements were performed before SWL. Vital signs and anthropometric measurements, including height, body weight, waist circumference, and body fat percentage were also assessed. Flow-mediated dilation of the brachial artery was evaluated in each subject with a Sonosite (Seattle, WA) ultrasound device post-forearm occlusion (5 minutes) in the supine state. Ultrasonic determinations of brachial artery diameter and continuous wave Doppler determination of blood flow velocity (BFV) were made above the antecubital fossa at baseline and 1, 2, and 3 minutes after forearm occlusion release. During analysis, the maximum percentage increase in diameter was recorded. For the SWL bout, subjects performed 6 sets of 10 repetitions of bilateral leg press exercise using maximum weight loads. Blood pressure was measured while holding the final repetition of each set. After the SWL bout, FMD of the brachial artery was reevaluated. In addition, sublingual NTG (0.4 mg) was used to determine EID post-exertion. Brachial artery dilator responses to NTG were measured at 2, 3, 4, and 5 minutes and the maximal percent dilation from baseline was recorded during analysis. Analyses of FMD, EID, and BFV of the brachial artery were performed off-line using edge-detection software (Medical Imaging; Iowa City, IA). To estimate brachial artery wall shear stress, peak shear rates (SR) were calculated during FMD using the following equation: peak SR = maximal

flow velocity (mm/s) ÷ diameter (mm). Flow-mediated dilation was normalized for the peak SR using the following equation: normalized FMD = FMD ÷ peak SR.

3. Analysis and Results

Differences in physical characteristics (lipid panels, glucose measurements, vital signs, and anthropometric measurements) between OB and LN subjects were compared using independent-samples t-tests. Linear regression analyses were conducted to investigate the association of obesity with brachial artery FMD, independent of potential confounding effects. The effects of acute exertion on brachial artery diameter, maximum percentage change in diameter (FMD), and normalized FMD were studied in OB and LN subjects separately, using paired samples t-tests. Independent samples t-tests were performed to compare differences in FMD change scores (pre- and post-exertion) and NTG responses post-exertion between OB and LN subjects. Pearson's correlations were used to evaluate how brachial artery reactivity to FMD and NTG responses relate to physical characteristics. The level of statistical significance for all analyses was set at $P < 0.05$. Data were analyzed using SPSS software (Version 19.0; SPSS Inc., Chicago, IL).

Subjects were normotensive with similar BP responses during the SWL bout (Table I). Baseline brachial artery diameters were similar between OB and LN subjects and were unaltered after the SWL bout (Table II). Baseline BFV and SR were significantly reduced in OB (64.4 ± 7.1 and 193.9 ± 21.0, respectively) compared to LN subjects (85.3 ± 5.5 and 267.2 ± 16.8, respectively, $p < 0.05$) before SWL. Flow-mediated dilation tended to be higher in OB (10.7 ± 0.4%) compared to LN subjects (8.5 ± 1.3%, $p = 0.11$) before SWL. When FMD was normalized for the peak SR, the difference in FMD between OB and LN subjects was significant (OB: 0.032 ± 0.003 and LN: 0.018 ± 0.004, $p < 0.05$) (Figure 5). After SWL, brachial artery

FMD was significantly reduced in OB subjects (8.3 ± 0.6%, $p < 0.01$) and tended to be reduced in LN subjects (LN: 6.4 ± 1.6%, $p = 0.2$) (Figure 5), however, the absolute change in FMD pre- and post-SWL was not significantly different (OB: -2.4 ± 0.6% and LN: -2.2 ± 1.6%, p = NS) (Figure 6). Brachial artery FMD in OB and LN subjects was not related to resting BPs, maximum BPs, total cholesterol, LDL cholesterol, or triglycerides. There were no differences in maximal blood flow velocities or peak SR between OB and LN subjects before or after acute exertion. Unexpectedly, NTG-induced dilation of the brachial artery (post-exertion) was lower in OB (21.6 ± 1.3%) compared to LN subjects (27.6 ± 2.1%, $p < 0.05$) and this response was negatively correlated with body weight independent of other physical characteristics ($r = -0.70$, $p = <0.01$) (Figure 7).

4. Summary

The results of this pilot study suggest that a single bout of strenuous weight lifting impairs endothelium-dependent vasodilation in obese and lean adults who are sedentary. In addition, endothelium-independent vasodilation to nitroglycerin is reduced in obese adults after a single bout of strenuous weight lifting and is associated with body weight independent of other CVD risk factors. Based on this study it appears that both endothelium-dependent and endothelium-independent vascular functions are altered by acute resistance exercise in obesity and that the mechanism of vascular dysfunction in obesity may be linked to a reduced sensitivity to NO.

As aforementioned, it is well documented that regular resistance exercise training is cardioprotective. However, it is questionable as to how many bouts of acute resistance exercise are necessary to reap the benefits of chronic resistance exercise. Therefore, an aim of the next phase of this research was to further understand the effects of resistance exercise training on

vascular function by examining the impact of repeated bouts of resistance exercise in previously sedentary individuals. For subsequent studies, we will focus specifically on sedentary adults who are obese. Obese individuals may express elevated concentrations of pro-atherogenic inflammatory adipokines and cytokines that impact vascular function. In addition, exercise training has been shown to induce significant benefits in individuals with elevated CVD risk factors compared to those without. Given these facts, sedentary obese adults may be more amendable to an exercise intervention. Furthermore, resistance exercise training may increase vascular release of, and sensitivity to NO in obesity.

Figure 3. The effects of a sedentary lifestyle and obesity on vascular function. Low shear stress evoked by a sedentary lifestyle impairs vascular function through oxidative stress-dependent reduction in nitric oxide (NO) production and these effects can manifest acutely after strenuous exertion (i.e. resistance exercise). In addition, these effects may be augmented in the presence of obesity since adverse alterations in production of pro- and anti-inflammatory adipokines and cytokines can reduce NO bioavailability and impair vascular function.

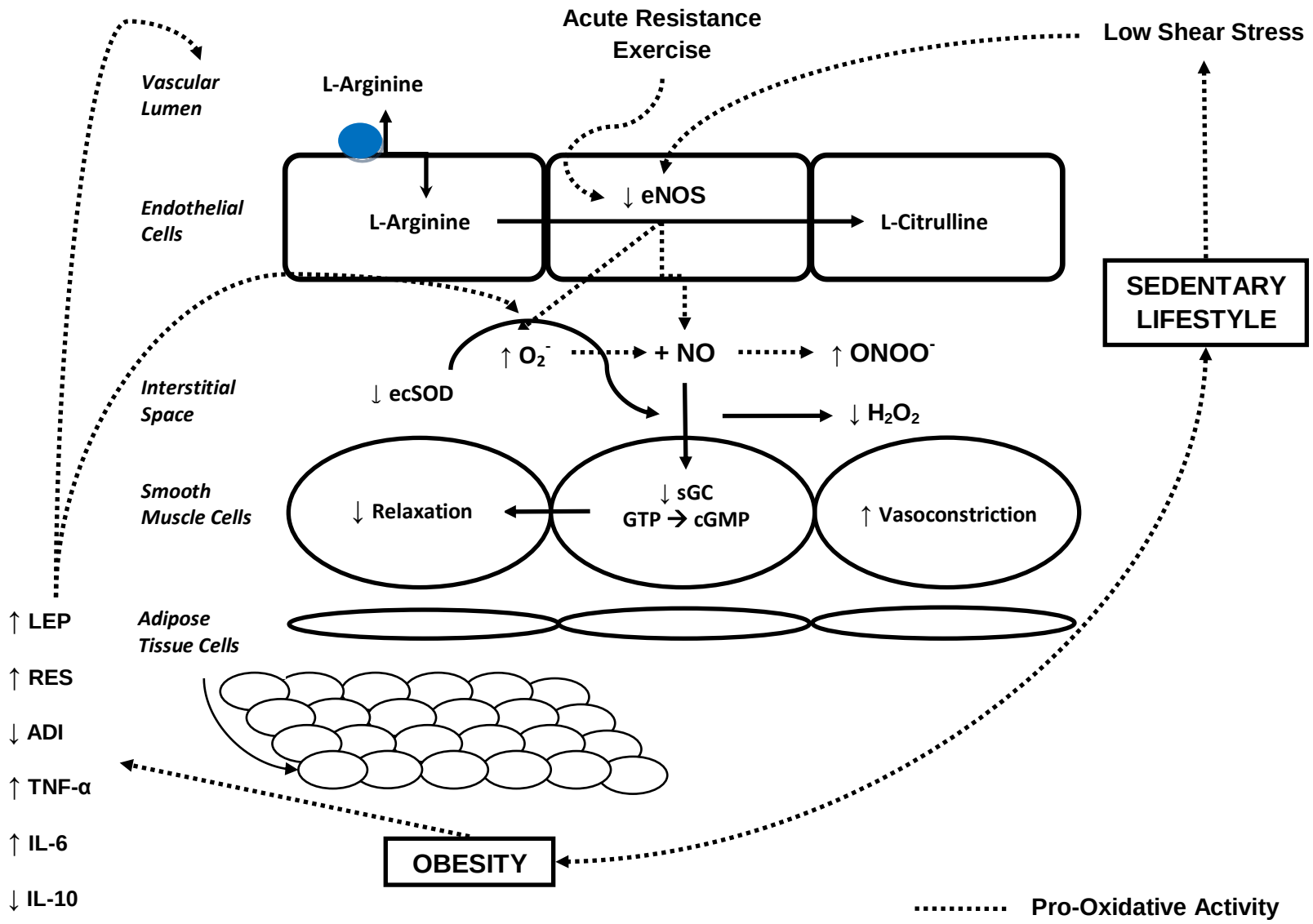

Acute Resistance Exercise
Low Shear Stress
Vascular Lumen
L-Arginine
Endothelial Cells
↓ eNOS
L-Arginine
L-Citrulline
SEDENTARY LIFESTYLE
↑ O_2^-
+ NO
↑ $ONOO^-$
Interstitial Space
↓ ecSOD
↓ H_2O_2
Smooth Muscle Cells
↓ Relaxation
↓ sGC
GTP → cGMP
↑ Vasoconstriction
Adipose Tissue Cells
↑ LEP
↑ RES
↓ ADI
↑ TNF-α
↑ IL-6
↓ IL-10
OBESITY
Pro-Oxidative Activity

Figure 4. Potential effects of resistance exercise training on obesity and vascular function. Regular resistance exercise training may attenuate oxidative stress-dependent reduction in nitric oxide (NO) production associated with a sedentary lifestyle and obesity through mechanisms that beneficially modulate adipokine and cytokine profiles. Resistance exercise training may also have a direct beneficial effect on eNOS activity and, consequently, NO production.

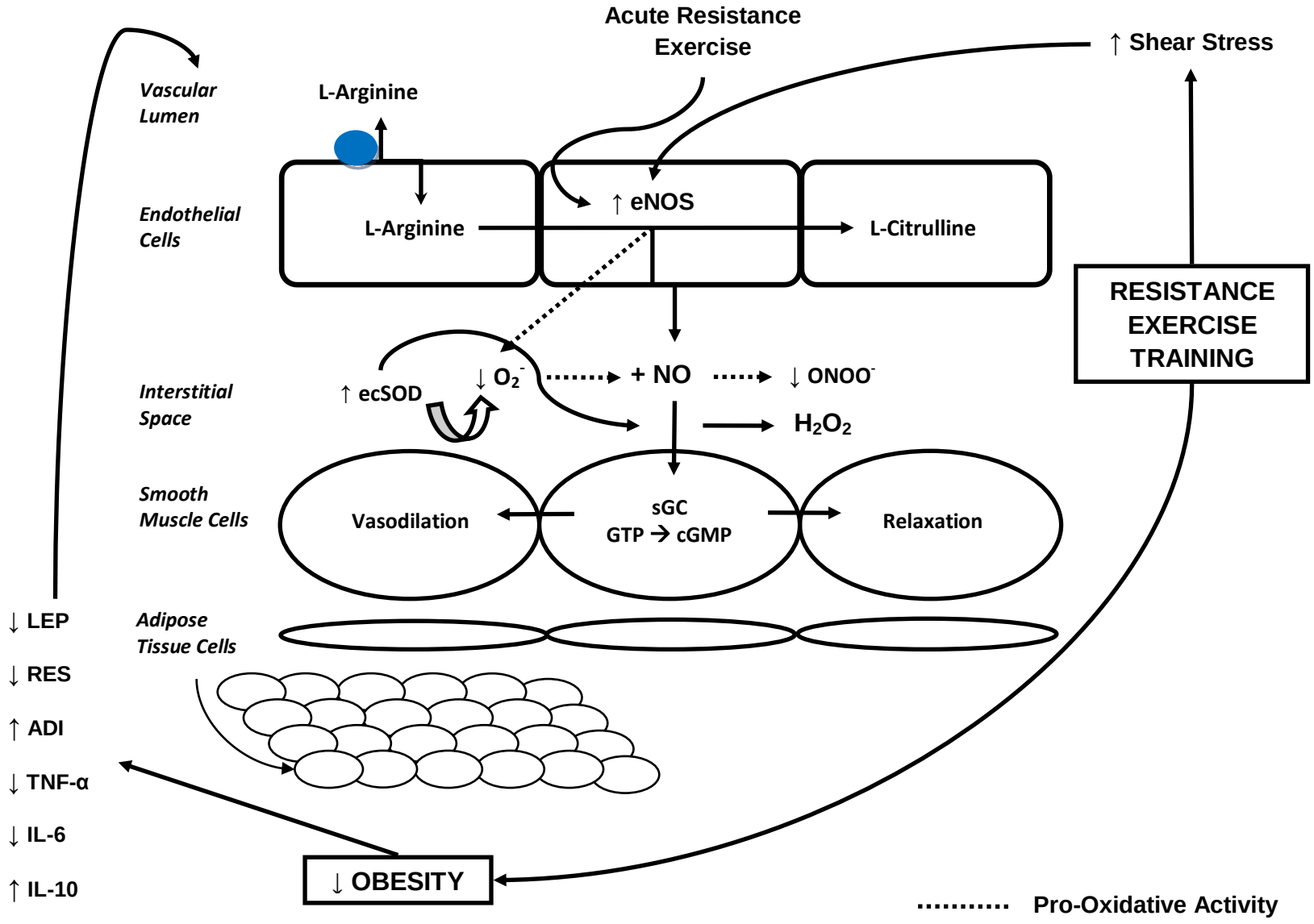

Acute Resistance Exercise
↑ Shear Stress
Vascular Lumen
L-Arginine
Endothelial Cells
↑ eNOS
L-Arginine
L-Citrulline
RESISTANCE EXERCISE TRAINING
Interstitial Space
↑ ecSOD
↓ O_2^-
+ NO
↓ $ONOO^-$
H_2O_2
Smooth Muscle Cells
Vasodilation
sGC
GTP → cGMP
Relaxation
Adipose Tissue Cells
↓ LEP
↓ RES
↑ ADI
↓ TNF-α
↓ IL-6
↑ IL-10
↓ OBESITY
Pro-Oxidative Activity

TABLE I

PHYSICAL CHARACTERISTICS FOR SEDENTARY WOMEN WHO UNDERWENT A SINGLE BOUT OF STRENUOUS WEIGHT LIFTING

	Lean (n = 8)	**Obese (n = 9)**
Height (cm)	164.7 ± 2.9	160.0 ± 2.6
Weight (kg)	58.4 ± 2.3	88.5 ± 5.3*
Body mass index ($kg \cdot m^{-2}$)	21.5 ± 0.5	34.2 ± 1.1*
Body fat %	27.3 ± 2.6	42.8 ± 1.5*
Waist circumference (cm)	71.7 ± 1.8	95.2 ± 2.6*
Total cholesterol (mg/dL)	154.8 ± 9.0	197.4 ± 12.5*
LDL cholesterol (mg/dL)	78.6 ± 6.3	115.8 ± 8.9*
HDL cholesterol (mg/dL)	62.9 ± 4.5	54.3 ± 3.6
Triglycerides (mg/dL)	66.5 ± 10.6	116.9 ± 21.4*
Glucose (mg/dL)	83.6 ± 3.3	87.4 ± 2.6
Maximum systolic BP (mm/Hg)	187.8 ± 9.1	188.5 ± 6.0
Maximum weight lifted (lb)	228.0 ± 8.5	236.0 ± 7.4

LDL, low-density lipoprotein; HDL, high-density lipoprotein; BP, blood pressure. Data are presented as mean ± SEM. *Significant difference at $P < 0.05$.

TABLE II

HEMODYNAMIC AND VASCULAR CHARACTERISTICS FOR SEDENTARY WOMEN WHO UNDERWENT A SINGLE BOUT OF STRENUOUS WEIGHT LIFTING

	Lean (n = 8)		Obese (n = 9)	
	Before SWL	After SWL	Before SWL	After SWL
Resting heart rate (beats/min)	65.0 ± 3.0	70.1 ± 3.4	69.7 ± 3.7	70.9 ± 3.6
Systolic BP (mm Hg)	103.8 ± 2.6	105.3 ± 3.6	119.9 ± 3.4†	115.1 ± 4.1
Diastolic BP (mm/Hg)	60.6 ± 1.2	63.9 ± 2.2	76.6 ± 3.2†	76.6 ± 2.4†
Baseline diameter (mm)	3.2 ± 0.1	3.1 ± 0.1	3.4 ± 0.1	3.4 ± 0.1
Brachial artery FMD (%)	8.5 ± 1.3	6.4 ± 1.6	10.7 ± 0.4	8.3 ± 0.6*
Baseline BFV (cm/s)	85.3 ± 5.5	90.5 ± 14.2	64.4 ± 7.1†	72.7 ± 8.6
Peak BFV (cm/s)	136.7 ± 14.4	140.7 ± 14.3	135.1 ± 12.6	143.4 ± 18.4
Baseline SR (s^{-1})	267.2 ± 16.8	287.8 ± 39.7	193.9 ± 21.0†	218.8 ± 30.3
Peak SR (s^{-1})	385.6 ± 46.1	421.1 ± 28.7	375.0 ± 41.3	404.9 ± 63.0
Normalized FMD	0.018 ± 0.004	0.011 ± 0.004	0.032 ± 0.003†	0.024 ± 0.003*
FMD Δ (%)	-2.2 ± 1.6		-2.4 ± 0.6	
Baseline NTG diameter (mm)	ND	3.1 ± 0.1	ND	3.4 ± 0.2
Maximum NTG diameter (mm)	ND	4.0 ± 0.2	ND	4.1 ± 0.2
Maximum NTG dilation (%)	ND	26.8 ± 2.1	ND	21.6 ± 1.3†

BP, blood pressure; FMD, flow-mediated dilation; SR, shear rate; BFV, blood flow velocity; FMD Δ, absolute change in FMD; NTG, nitroglycerin; ND, not determined. Data are presented as mean ± SEM. *Significant difference observed after SWL versus before SWL ($P < 0.05$). †Significant difference observed in Obese versus Lean ($P < 0.05$).

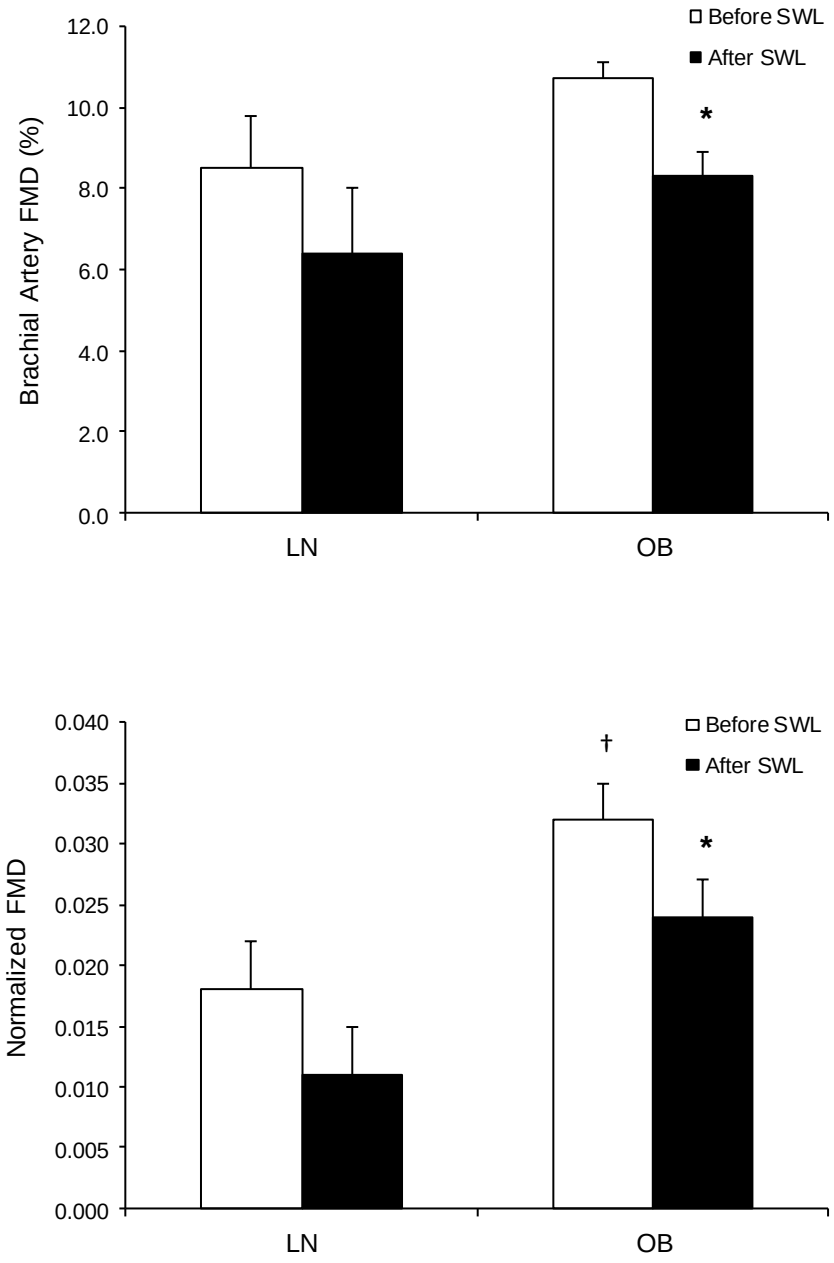


Figure 5. The effect of a single bout of strenuous weight lifting (SWL) on brachial artery flow-mediated dilation (FMD) (top panel) and normalized FMD (bottom panel) in lean (LN) and obese (OB) sedentary women. *Significant difference observed after SWL versus before SWL ($p < 0.05$). †Significant difference observed in OB versus LN ($P < 0.05$).

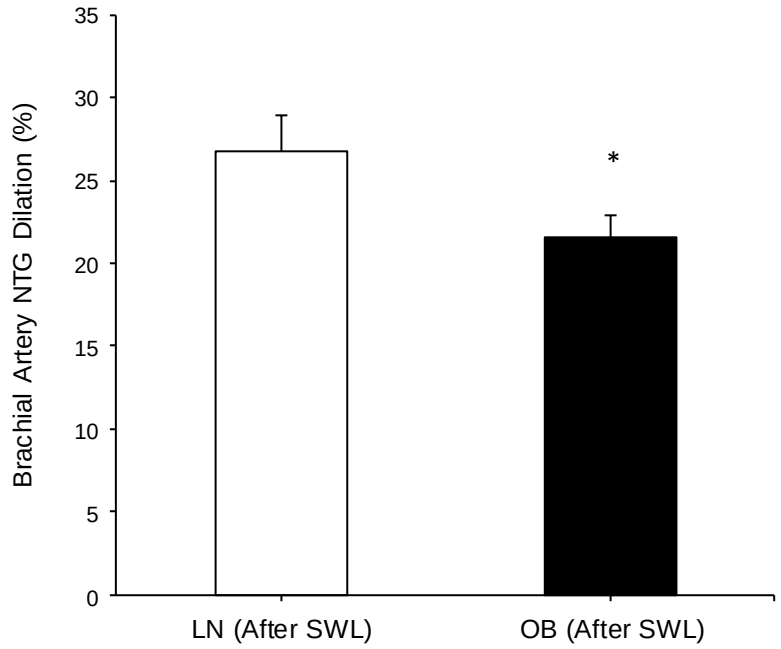


Figure 6. Nitroglycerin (NTG)-induced dilation of the brachial artery in lean (LN) and obese (OB) sedentary women after a single bout of strenuous weightlifting (SWL). *Significant difference observed in OB versus LN ($p < 0.05$).

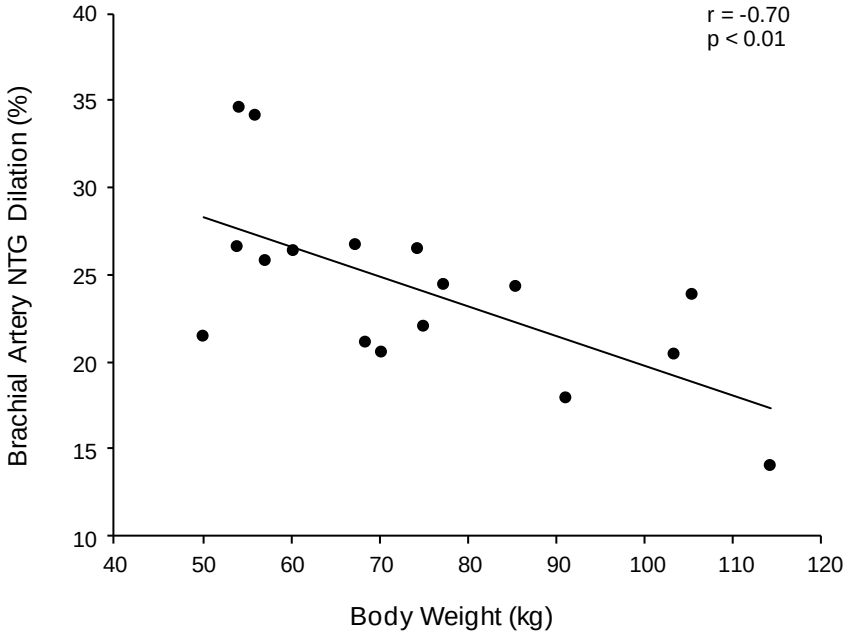


Figure 7. Correlation between body weight and nitroglycerin (NTG)-induced dilation of the brachial artery in sedentary women after a single bout of strenuous weight lifting (SWL).

III. METHODS

A. Overview of Research Design

A within-subject, repeated measures design was implemented. This research design consisted of methods aimed to: 1) examine the effects of acute exertion on vascular function and circulating adipokine and cytokine levels in sedentary OB adults, and 2) determine if an 8-week moderate-intensity RET intervention improves vascular responses to acute exertion in sedentary OB adults. Our first hypothesis was that acute exertion would impair vascular function in sedentary OB adults and that this impairment would be associated with increased circulating levels of LEP, RES, TNF-α, and IL-6, and reduced circulating levels of ADI and IL-10. The secondary hypothesis was that 8 weeks of RET would protect against acute exertion-induced impairment of vascular function and changes in circulating adipokine and cytokine levels would be involved in the improved vascular response.

Subjects were evaluated at four time points within a 12-week study period: 1) baseline, 2) pre-training (two weeks after baseline), 3) midpoint (four weeks after pre-training), and 4) follow-up (four weeks after midpoint). At each time point subjects underwent a single bout of SWL designed to increase BP. To test the first hypothesis, vascular function was assessed before and after SWL using brachial artery FMD. Brachial artery FMD was measured by ultrasound with two-dimensional imaging and continuous wave Doppler for determination of BFV and SR. Blood samples were also obtained from subjects at each time point before and immediately after SWL for measurement of circulating adipokine and cytokine levels. Three adipokines (LEP, RES, and ADI) and three cytokines (TNF-α, IL-6, and IL-10), were measured in serum along with red and white blood cells, platelets, hemoglobin, and hematocrit, in order to examine

potential inflammation-related mechanisms underlying VD after acute exertion. To test the secondary hypothesis, a whole-body RET intervention was carried out between time points 2 and 4. All subjects underwent RET twice weekly for 8 weeks (Figure 8).

Other relevant physical and physiological variables assessed at baseline (time point 1) and/or during follow-up (time point 4) include: fasting lipids and glucose, anthropometrics, body composition, daily physical activity, functional capacity (peak VO_2), muscular strength, and dietary patterns. The primary outcome variable was the absolute change of brachial artery FMD (before and after SWL) from baseline to follow-up. Secondary outcome variables included changes in circulating adipokine and cytokine levels, circulating blood components, peak BFV, peak SR, BP, anthropometrics, body fat percentage, and metabolic risk factors.

B. Subjects

Twenty adults were recruited to participate in this research study. Inclusion criteria were: 1) 18 to 40 years of age, 2) obese, defined as having a BMI between 30.0 and 40.0 kg/m^2; 3) maintenance of stable body weight (less than 10 percent body weight change) for at least 12 months prior to enrollment; 4) sedentary, defined as engaging in less than 30 minutes of moderate physical activity per day for at least 6 months prior to enrollment; and 5) no history of RET or AET within the past 6 months prior to enrollment.

Exclusion criteria were: 1) acute medical illness or injury (past 6 months); 2) use of medications that could alter study results, including antihypertensive, lipid-lowering or anticoagulant medications; 3) metabolic or cardiovascular disorders including diagnosis of diabetes mellitus, unstable angina or congestive heart failure; 4) neurological disorders; 5) current pregnancy (past 6 months) or lactation (past 2 months); 6) hypertension (BP greater than 140/90 mmHg); 7) hyperlipidemia (total cholesterol greater than 230 mg/dL and triglycerides

greater than 200 mg/dL); 8) history of anemia (hemoglobin less than 8 mg/dL); 9) tobacco use (past 6 months); 10) known thyroid, pituitary or coagulation disorders; 11) known kidney or liver disease; 12) current eating disorder; 13) history of cancer; 14) orthopedic pathology or deformity; 15) history of gout; 16) known adverse reactions to nitroglycerin or lidocaine; 17) use of Viagra or other erectile dysfunction medications within 24 hours of study participation; 18) current abuse of alcohol or illicit drugs; and 19) current participation or planned enrollment in a formal weight loss program during the study period.

C. Recruitment

Subjects were recruited from UIC and communities surrounding Chicago through flyer postings, newsletters, and the UIC Announce system. There was no intention to focus on, or exclude, any particular gender, ethnicity, or race. Subjects were recruited to approximate the distribution of the city of Chicago as listed in the 2010 census—31.7% Caucasian, 32.9% Black, 28.9% Hispanic, 5.5% Asian/Pacific Islander, 0.5% Native American, 0.5% Other. Since this research study involved assessment of vascular function after SWL with significant elevations in BP, children were not included in order to rule out potential confounding effects of an immature cardiovascular system on vascular responses to acute exertion.

Subjects were initially pre-screened by telephone and when all major inclusion criteria were met, an in-person screening was scheduled during which time eligibility criteria for enrollment were confirmed upon completion of a medical and exercise history questionnaire, a physical examination, and analyses of urine and blood samples. Written informed consent was obtained from all subjects prior to their participation. The study protocol was approved by the Office for the Protection of Research Subjects and the IRB at UIC.

D. Experimental Design and Procedures

Experiments and assessments for all four time points (baseline, pre-training, midpoint, and follow-up) were conducted at UIC in the Clinical Research Center (CRC). Measurements were made in a temperature-controlled room at a similar time of day for each visit. Protocols and procedures for the RET intervention were carried out in the Muscle Performance Laboratory in the Department of Physical Therapy at the College of Applied Health Sciences (AHS).

1. Baseline

Subjects deemed eligible after the telephone pre-screening were invited for the baseline (screening) visit during which time they underwent a medical exam to verify enrollment criteria. We also conducted baseline assessments during this visit to examine the effects of acute exertion on vascular function and circulating adipokine and cytokine levels in OB subjects.

Medical Exam. Prior to the medical exam, subjects were asked to refrain from eating and drinking (except water) for at least 12 hours. Written informed consent was obtained from all subjects before participation after which the following procedures were executed: completion of a medical and exercise history questionnaire, completion of a brief food questionnaire, a urine pregnancy test if indicated, assessment of vital signs (resting heart rate (HR) and BP), anthropometric measurements (height, weight, BMI, and waist circumference (WC)), and body fat analysis. Fasting blood samples were also collected using venipuncture for laboratory analysis of lipids and glucose as well as red and white blood cells, platelets, hemoglobin, and hematocrit. During the blood draw, additional samples were collected in red-top tubes for measurement of serum levels of three adipokines (LEP, RES, and ADI) and three cytokines (TNF-α, IL-6, and IL-10) at baseline using previously described enzyme-linked immunosorbent

assay (ELISA) techniques (124). Serum was separated and frozen at -25°C for subsequent analysis.

Baseline Assessments. Immediately after the medical exam and initial blood collection, subjects underwent a baseline ultrasound examination for evaluation of brachial artery FMD. After FMD was assessed, subjects underwent a single bout of SWL with BP and exercise HR measurements. Additional blood samples were collected during the 30 minutes of recovery from SWL for subsequent analysis of red and white blood cells, platelets, hemoglobin, and hematocrit as well as serum levels of LEP, ADI, TNF-α, IL-6, and IL-10 post-exertion. Subjects were then reevaluated for brachial artery FMD. Approximately 10 minutes after the second FMD assessment (post-exertion), subjects were given one tablet of sublingual NTG (0.4 mg) to induce EID of the brachial artery.

Upon completion of baseline assessments and data collection procedures, each subject was given a pedometer. The pedometer measures daily physical activity by recording the number of steps taken in walking. Subjects were asked to wear the pedometer during their waking hours to help them track their physical activity. No specific exercise instructions were provided at this time point but subjects were asked to continue their normal physical activities and daily diet.

Assessment of Vital Signs. Blood pressure and resting HR were measured using an automatic monitor (Welch Allyn Vital Signs Monitor 300 Series; Welch Allyn Inc, Skaneateles Falls, NY) with an appropriate cuff size. Measurements were made on the non-dominant arm after subjects were in the supine position for at least 5 minutes. Two readings were taken and averaged for BP and resting HR measurements.

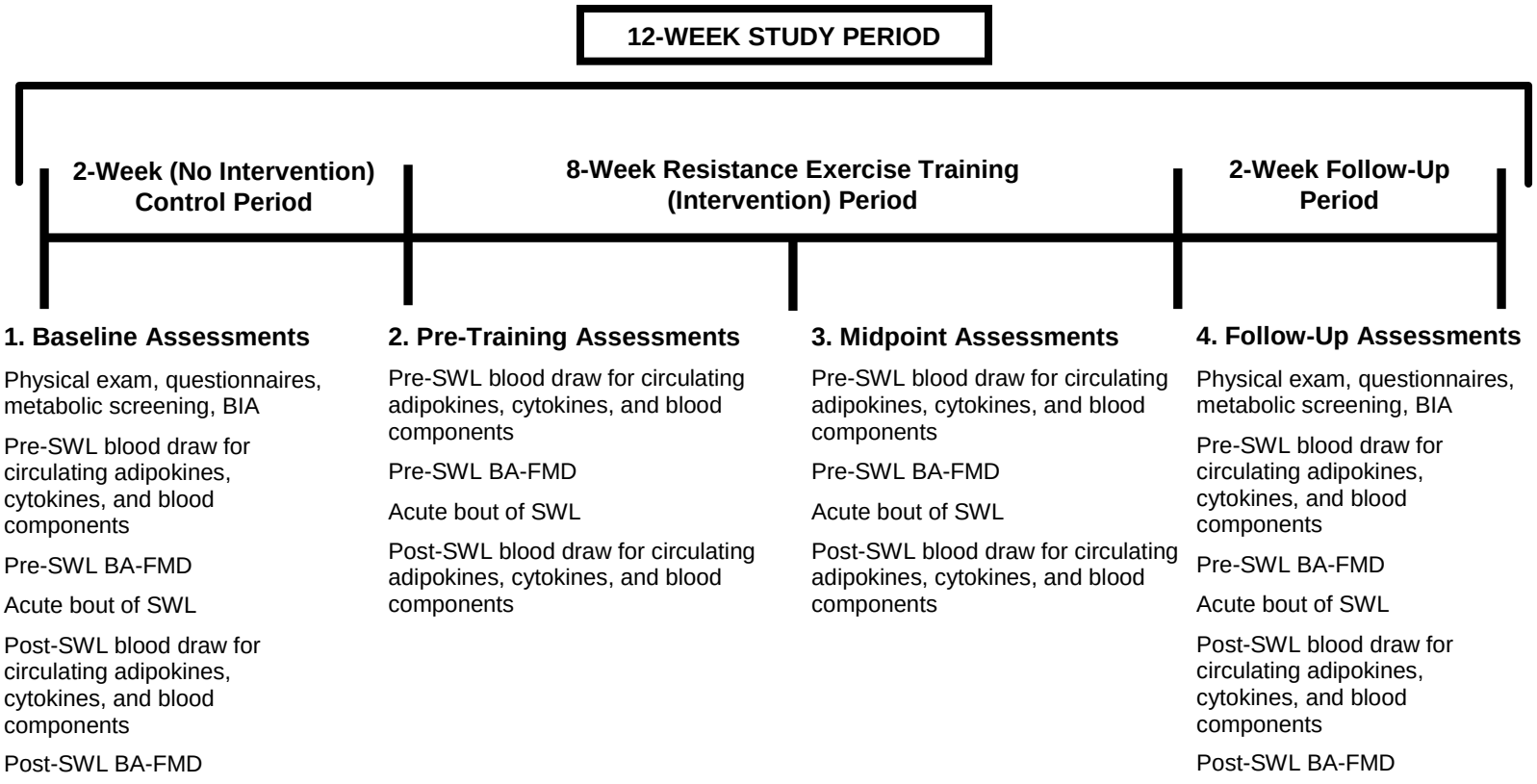


Figure 8. Twelve-week research study timeline. Subjects were evaluated at four time points: 1) baseline, 2) pre-training (two weeks after baseline), 3) midpoint (four weeks after pre-training), and 4) follow-up (four weeks after midpoint).

Anthropometric Measurements and Body Fat Analysis. Height (cm) and weight (kg) were measured using a rigid stadiometer and a calibrated scale while subjects were wearing light clothing. Body mass index was calculated using the following equation: BMI = body mass (kg) / stature (m^2). Waist circumference (cm) was assessed with a Gulick tape measure at the narrowest part of the waist (above the umbilicus and below the xiphoid process) (127-129). Previous studies have shown that waist circumference can be used to estimate visceral obesity (52), and predicts VD independent of other cardiovascular risk factors (130). Duplicate WC measurements were taken in nonconsecutive order and the average was recorded. Body composition was determined by bioelectrical impedance analysis (BIA) (RJL Systems Quantum Series; RJL Systems, Inc; Clinton Township, MI) while subjects were in a hydrated state. The BIA machine generates a current which passes through the body by way of electrodes situated on the hands and feet. The electrical resistance to the flow of the current through body tissues is then used to calculate an estimate of total body water after which total body water is used to estimate fat-free mass. The standard error of BIA is approximately 4% (131,132).

Metabolic Risk Factors and Circulating Blood Components. Plasma was separated by centrifugation for off-site laboratory analysis of lipids and glucose as well as red and white blood cells, platelets, hemoglobin, and hematocrit (Alverno Clinical Laboratories, LLC; Hammond, IN). Lipids including total cholesterol, high-density lipoproteins (HDLs), low-density lipoproteins (LDLs), and triglycerides were measured using spectrophotometric assays. Glucose concentration was measured using the glucose oxidase procedure (Beckman Autoanalyser II; Beckman Coulter Inc; Fullerton, CA). Complete blood counts (CBCs) were performed using automated hematology analysis (Beckman Coulter LH 750; Beckman Coulter Inc; Fullerton,

CA) to access circulating levels of red and white blood cells, platelets, hemoglobin, and hematocrit.

Serum Adipokine and Cytokine Measurements. Serum levels of three adipokines (LEP, RES, and ADI) and three cytokines (TNF-α, IL-6, and IL-10) were quantified by means of commercial high-sensitivity ELISA kits (Quantikine HS; R&D Systems Inc; Minneapolis, MN) which were used according to the manufacturer's instructions. Briefly, a sandwich technique of ELISA was employed for each of the adipokine and cytokine measurements. A monoclonal antibody specific for the analyte of interest (LEP, RES, ADI, TNF-α, IL-6, or IL-10) was pre-coated onto each microplate. Standards and samples were pipetted into a 96-welled kit so that any of the analyte present could bind to an immobilized antibody. After following the manufacturer's washing steps to remove interfering molecules and unbound substances, an enzyme-linked polyclonal antibody specific for the analyte of interest was added to the wells to "sandwich" the analyte that was immobilized during the first incubation. Any unbound antibody-enzyme reagent was washed from the wells and a substrate solution was then added to the wells. After an incubation period, an amplifier solution was also added to the wells so that color could develop. The intensity of the color was directly related to the amount of the analyte bound. After the color development was stopped the intensity of the color was measured with a standard ELISA plate reader.

Brachial Artery Flow-Mediated Dilation. Nitric oxide-mediated vascular function was assessed by measuring FMD of the brachial artery using techniques patterned after those of Celermajer and colleagues (5). In premenopausal women, FMD may vary during the menstrual cycle (133); therefore, measurements were performed in the early follicular phase of menses when possible. Brachial artery FMD was measured while subjects were in the supine position.

For FMD determination, ultrasound imaging (Sonosite; Seattle, WA) of the brachial artery was performed in a longitudinal plane at a site one to three centimeters proximal to the antecubital fossa of the dominant arm (134). Baseline images were recorded after which a cuff attached to a sphygmomanometer was placed on the forearm and inflated to 50 mmHg above systolic BP for 5 minutes. Brachial artery diameter (mm) was determined during peak hyperemia after release of the cuff. To assess dilation, at least 30 seconds of images were captured during the first, second, and third minutes after cuff release. Blood pressure and HR were measured at baseline, during, and after FMD. Flow velocity was recorded at baseline and just after cuff release where maximal velocity was observed. Approximately 10 minutes after reactive hyperemia, EID was induced with 0.4 mg of sublingual NTG. At least 30 seconds of images were captured during each minute after NTG administration for a total of 5 minutes. Blood pressure and HR were measured before and during NTG-induced vasodilation. All ultrasonographic images were recorded directly to the device and subsequently transferred to a password protected computer.

Strenuous Weight Lifting Protocol. The SWL protocol involved performance of a single bout of bilateral lower-body weight lifting using an isotonic variable-resistance leg press machine (Hoist HD-1610 Selectorized Leg Press; Hoist Fitness Systems; San Diego, California). This protocol was designed to elicit equal increases in BP between subjects (26,135). After becoming familiarized with the leg press machine subjects performed 1 to 2 sets of 10 repetitions at a perceived capacity of approximately 30 to 40% of 1-repetition maximum (RM). Subjects then performed 3 to 4 sets of 10 repetitions at a perceived capacity of approximately 80 to 90% of 1-RM. During the final repetition of each set, subjects executed an isometric hold while BP was measured using a sphygmomanometer. A 2-min rest interval was allotted between each set. Exercise heart rate and the 10-point Borg rating of perceived exertion (RPE) scale were used as

indices of intensity after each set and weight was added as tolerated. The maximum weight lifted for the SWL bout was determined within 20 minutes.

2. Pre-Training

Approximately 2 weeks after the screening/baseline visit, OB subjects deemed eligible for the full study returned to the CRC to undergo pre-training assessments. The 2-week time period between baseline and pre-training (1st and 2nd time points) served as a "no-intervention" control period after which we reevaluated the effects of acute exertion on vascular function and circulating adipokine and cytokine levels in subjects just prior to initiation of the RET intervention. Baseline fitness testing and RET orientation were also conducted at this time point.

Pre-Training Assessments. For pre-training assessments, subjects underwent procedures similar to those conducted at baseline. Initially, a urine pregnancy test was performed (if indicated) and vital signs (resting HR and BP) were assessed. Blood samples were then collected using venipuncture for laboratory analysis of red and white blood cells, platelets, hemoglobin, and hematocrit. During the blood draw, additional samples were collected in red-top tubes for measurement of LEP, RES, ADI, TNF-α, IL-6, and IL-10 using ELISA. Serum was separated and frozen at -25°C for subsequent analysis. Immediately after blood collection, subjects underwent another baseline ultrasound examination for evaluation of brachial artery FMD pre-exertion. After brachial artery FMD was assessed, subjects underwent a second bout of SWL with BP and exercise HR measurements. Additional blood samples were collected during the 30 minutes of recovery from this bout of SWL for subsequent analysis of red and white blood cells, platelets, hemoglobin, and hematocrit as well as serum levels of LEP, RES, ADI, TNF-α, IL-6, and IL-10 post-exertion. Subjects were then reevaluated for brachial artery FMD.

Approximately 10 minutes after the second FMD assessment (post-exertion), subjects were given one tablet of sublingual NTG to induce EID of the brachial artery.

Baseline Fitness Testing and Orientation. Within one week of pre-training assessments OB subjects arrived at the Muscle Performance Laboratory to undergo baseline fitness testing and RET orientation during which time specific exercise instructions were provided. For fitness testing, subjects underwent a standard submaximal exercise stress test on a cycle ergometer which was used as an estimate of peak VO_2. In addition, multiple-RM tests were conducted for various exercises based on a goal of 10 repetitions. These 10-RM tests were used to access muscular strength and obtain all necessary information for assigning individualized loads for the RET intervention. For orientation, subjects were educated on the principles of RET and became familiarized with the equipment. Subjects were also supplied with training logs to be utilized during each exercise session and taught to record the exercise type, weight lifted, and number of repetitions and sets completed.

Submaximal Cycle Ergometer Testing. Submaximal exercise stress tests were performed using the YMCA cycle ergometer protocol (136) This is a multistage protocol involving progressive increases in workload based on exercise HR responses. All stress tests were performed under standardized conditions in a stable laboratory environment. Initially, subjects were given adequate explanation of the exercise testing protocol which consisted of three to four consecutive 3-minute stages. Subjects were then seated on a precalibrated cycle ergometer (Monark Ergomedic 828E; Monark Exercise; Varberg, Sweden) and instructed to perform a 1-minute warm-up with a workload of 0 Watts at a speed of 50 revolutions per minute (rpm) in order to become familiar with the machine and the speed. The ergometer was subsequently set to a workload of 25 Watts (first workload) so that the first 3-minute stage could begin. Subjects

were instructed to continue the speed of 50 rpm. Heart rate was recorded during the last 30 seconds before the end of the 2nd and 3rd minutes and readings were multiplied by two in order to estimate the exercise HR of each minute. If the difference between the 2nd and 3rd minutes was greater than 5 beats per minute (bpm), the above step was repeated into the 4th minute and so on until the exercise HR became steady. When the first workload was finished subjects proceeded to the next workload level. The workload of the following stage was dependent on the first workload performance as follows: 50 to 125 Watts for the 2nd workload, 75 to 150 Watts for the 3rd workload, and 100 to 175 Watts for the 4th workload (i.e. the larger the exercise HR response, the smaller the workload increase). The test continued until two HR readings between 110 and 150 bpm were recorded. At this point, the ergometer workload was set back to 25 Watts for a cool-down period. The subject's peak VO_2 was calculated by inserting the workloads and HRs for the final two stages of the protocol into a multistage VO_2 max prediction equation (137).

Ten-Repetition Maximum Testing. Ten-RM tests were conducted for eight different exercises using isotonic variable-resistance machines attached to a multi-station unit (Hoist HMG-4000 5 Station Modular Multi-Station; Hoist Fitness Systems; San Diego, California) (138). The 10-RM was chosen because the actual RET program implemented a higher number of repetitions (8 to 12) and since there is such extreme musculoskeletal loading associated with the standard 1-RM, we believed that this type of test would not be appropriate for a sedentary obese population. The following exercises were performed for the 10-RM tests: vertical chest press, mid row, lat pulldown, shoulder press, leg press, toe raise, leg extension, and leg curl. Ten-RM for the vertical chest press (upper body) and leg press (lower body) were recorded for the muscular strength evaluation and all other exercises were used for assigning initial loads. To determine 10-RM for each exercise, subjects initially completed a number of repetitions

(approximately 15 to 20) with submaximal resistance before selecting an initial load within their perceived capacity (approximately 50% of 1-RM). Ten-RM was determined within four trials during which resistance was progressively increased by 5 to 10 percent for upper body exercise or 10 to 20 percent for lower body exercise until failure occurred at 10 repetitions. For consistency between trials all repetitions were performed at the same speed of movement and range of motion (ROM). The load lifted successfully for 10 repetitions was recorded as the 10-RM.

Resistance Exercise Training Intervention. The American College of Sports Medicine (ACSM) and American Heart Association (AHA) guidelines recommend the inclusion of RET for healthy people of all ages and many individuals with chronic diseases, including CVD. The RET intervention was designed in accordance with their guidelines for individuals between the ages of 18 and 65 years who are generally healthy (139).

Subjects began the RET intervention within three days after orientation. The RET protocol was conducted twice weekly for 8 weeks with at least 48 hours between exercise sessions. Each session began with a 5-minute warm-up of aerobic exercise performed on a treadmill, stair stepper, or stationary cycle, and flexibility exercises targeting the major muscle groups to be trained. Following the warm-up, 8 to 10 dynamic-resistance exercises were performed using free weights and isotonic variable-resistance machines to target the following major muscle groups: quadriceps, hamstrings, gluteals, latissimus dorsi, rhomboids, pectorals, deltoids, biceps, and triceps. For each exercise, a moderate-intensity training load was set as a percentage of each subject's 10-RM which corresponds to approximately 65 to 75 percent of 1-RM. At this initial load, subjects performed 2 to 3 sets of 8 to 10 repetitions to the point of volitional fatigue while maintaining proper form. Adjustments were made to initial loads based

on the observation of ease or difficulty a subject experiences lifting the load for the required repetitions. Each repetition of exercise included slow, controlled muscle contractions of a moderate duration (2 seconds concentric and 4 seconds eccentric), one full inspiration and expiration, and no Valsalva maneuver.

For progression at 8 to 10 repetitions, the training load was incremented throughout the training period. If the subject could perform 2 or more repetitions over 10 repetitions in the last set in two consecutive workouts for a certain exercise, resistance was added to that exercise for the next session. This progression protocol ensured that volitional fatigue occurred between 8 and 10 repetitions. Each session ended with abdominal and lower-back exercises and a 5-minute cool-down using flexibility exercises employed during the warm-up.

3. Midpoint

After approximately 4 weeks of participation in the RET intervention, OB subjects underwent midpoint assessments. The time period between pre-training and midpoint (2nd and 3rd time points) served as the first of two "intervention" periods for which we evaluated the effects of RET on vascular responses to acute exertion in OB subjects.

For midpoint assessments, subjects underwent procedures identical to those conducted during the pre-training visit. Initially, a urine pregnancy test was performed (if indicated) and vital signs (resting HR and BP) were assessed. Blood samples were then collected using venipuncture for laboratory analysis of red and white blood cells, platelets, hemoglobin, and hematocrit. During the blood draw, additional samples were collected in red-top tubes for measurement of LEP, RES, ADI, TNF-α, IL-6, and IL-10 using ELISA. Serum was separated and frozen at -25°C for subsequent analysis. Immediately after blood collection, subjects underwent a third baseline ultrasound examination for evaluation of brachial artery FMD pre-

exertion. After brachial artery FMD was assessed, subjects underwent a third bout of SWL with BP and exercise HR measurements. Additional blood samples were collected during the 30 minutes of recovery from this bout of SWL for subsequent analysis of red and white blood cells, platelets, hemoglobin, and hematocrit as well as serum levels of LEP, RES, ADI, TNF-α, IL-6, and IL-10 post-exertion. Subjects were then reevaluated for brachial artery FMD. Approximately 10 minutes after the FMD assessment (post-exertion), subjects were given one tablet of sublingual NTG to induce EID of the brachial artery.

4. <u>Follow-Up</u>

After 8 weeks of participation in the RET intervention, OB subjects underwent a 2-week follow-up period. The time period between pre-training and follow-up (2nd and 4th time points) served as the second of the two "intervention" periods for which we evaluated the effects of RET on vascular responses to acute exertion in OB subjects. During the first week of follow-up, subjects underwent a second submaximal exercise stress test on a cycle ergometer to serve as an estimate of peak VO_2 post-RET. Ten-RM tests were also repeated to access changes in muscular strength as a result of the RET intervention. For the second week of follow-up, subjects returned to the CRC to undergo all procedures conducted at baseline (1st time point).

Initially, a urine pregnancy test was performed (if indicated) after which the following procedures were executed: assessment of vital signs (resting HR and BP), anthropometric measurements (height, weight, BMI, and WC), and body fat analysis. Fasting blood samples were also collected using venipuncture for laboratory analysis of lipids and glucose as well as red and white blood cells, platelets, hemoglobin, and hematocrit, post-RET. During the blood draw, additional samples were collected in red-top tubes for measurement of LEP, RES, ADI,

TNF-α, IL-6, and IL-10 using ELISA. Serum was separated and frozen at -25°C for subsequent analysis.

Immediately after blood collection, subjects underwent a final baseline ultrasound examination for evaluation of brachial artery FMD pre-exertion. After brachial artery FMD was assessed, subjects underwent the last bout of SWL with BP and exercise HR measurements. Additional blood samples were collected during the 30 minutes of recovery from this bout of SWL for subsequent analysis of red and white blood cells, platelets, hemoglobin, and hematocrit as well as serum levels of LEP, RES, ADI, TNF-α, IL-6, and IL-10 post-exertion. Subjects were then reevaluated for brachial artery FMD. Approximately 10 minutes after the FMD assessment (post-exertion), subjects were given one tablet of sublingual NTG to induce EID of the brachial artery.

E. Data Analysis

The primary outcome variable was the absolute change in brachial artery FMD (before and after SWL) from baseline and across the 12-week study period during which the RET intervention was implemented. Secondary outcome variables included changes in circulating adipokine and cytokine levels, circulating blood components, peak BFV, peak SR, normalized FMD, vital signs at rest and during acute exertion, anthropometric measurements, body fat percentage, and metabolic risk factors. Additional variables assessed included daily physical activity, peak VO_2, muscular strength, and dietary patterns.

1. Power Analysis

Sample size was estimated for comparison of differences in brachial artery FMD within subjects before and after a single bout of SWL. A paired t-test was used for the estimation. In order to achieve 80% power to detect a difference of at least 50% at a 5% significance level, a

sample of at least 8 subjects was required. Assuming a 20% drop-out rate, we aimed to recruit at least 10 subjects.

2. Statistical Analysis

All results are expressed as mean ± SEM. Repeated measures analysis of variance (ANOVA) was used to assess differences in brachial artery FMD (before and after SWL) across four time points (baseline, pre-training, midpoint, and follow-up) in the 12-week study period. Differences in circulating adipokine and cytokine levels, red and white blood cells, platelets, hemoglobin, and hematocrit, peak BFV, peak SR, normalized FMD, and vital signs before and after SWL were also compared across the four time points using ANOVA with repeated measures. When significant or interaction effects were found with ANOVA, post hoc comparisons were made with Bonferroni correction. Paired t-tests were used to compare anthropometric measurements, body fat percentage, metabolic risk factors, daily physical activity patterns, estimated peak VO_2, and muscular strength before and after the RET intervention. Subjects' dietary patterns prior to the RET intervention were compared using a one-sample t-test. Pearson correlations were used to examine relationships between subjects' vascular characteristics, circulating adipokine and cytokine levels, circulating blood components, peak BFV, peak SR, normalized FMD, and vital signs before and after SWL at any time point as well as anthropometric measurements, body fat percentage, metabolic risk factors, estimated peak VO_2, daily physical activity, and dietary patterns at baseline and/or follow-up. The level of statistical significance for all analyses was set at $P < 0.05$. Data were analyzed using SPSS software (Version 17.0; SPSS Inc., Chicago, IL).

IV. RESULTS

The major purpose of this study was to determine if 8 weeks of moderate-intensity RET improves vascular responses to acute exertion during a single bout of SWL in OB adults. We also examined whether or not there were any changes in circulating adipokine and cytokine levels in OB adults as a result of the RET intervention. The central hypothesis was that RET would protect against acute exertion-induced impairment of vascular function in OB adults by decreasing circulating levels of LEP, RES, TNF-α, and IL-6, and increasing circulating levels of ADI and IL-10. To test this hypothesis, OB adults served as their own controls and were evaluated at four time points within a 12-week study period (Figure 8). The primary outcome variable was the absolute change in brachial artery FMD (before and after SWL) from baseline across the study period. Secondary outcome variables included changes in circulating adipokine and cytokine levels, circulating blood components, peak BFV, peak SR, normalized FMD, BP, anthropometrics, body fat percentage, and metabolic risk factors. Functional capacity, muscular strength, and dietary patterns were also assessed.

Twenty OB subjects (2 men, 18 women) were enrolled in this research study. Three subjects (1 man, 2 women) failed the initial screening examination and could not participate. In addition, 5 subjects (1 man, 4 women) failed to return after the initial screening visit; therefore, their data are not included. Two subjects (both women) withdrew from the research study due to unrelated medical reasons that prevented them from completing the RET intervention. Therefore, a total of 10 OB women (mean age 30 years) completed the entire study and greater than 95 percent compliance with the RET intervention was achieved (i.e. at least 15 out of the 16 sessions attended) (Figure 9).

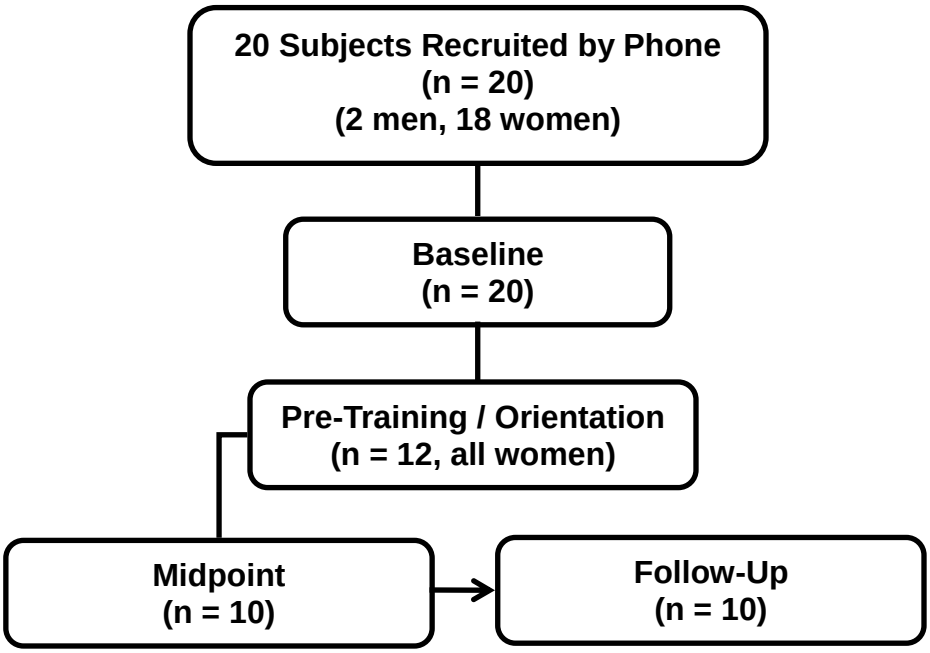


Figure 9. Flow diagram of subject participation at four time points.

A. Physical Characteristics, Blood Pressures, and Metabolic Risk Factors

There were significant differences between subjects' dietary patterns prior to participating in the RET intervention (Table V). However, Pearson correlations showed that these differences were not related to any other outcome variables assessed at baseline (1st time point). Physical characteristics, blood pressures, and metabolic risk factors for OB women at baseline and after 8 weeks of RET (4th time point) are presented in Table III. The RET intervention resulted in significant reductions in body fat percentage (42.9 ± 1.3 vs. 40.1 ± 1.5, p

= 0.049) and waist circumference (95.3 ± 2.3 vs. 92.6 ± 2.5, p = 0.001) as well as a significant increase in peak VO_2 (31.8 ± 0.9 vs. 34.0 ± 0.8, p = 0.002). There were also significant increases in daily physical activity, as measured in steps taken by a pedometer (5619.8 ± 204.2 vs. 6279.3 ± 150.3, p = 0.013) as well as increases in upper and lower body strength as assessed by 10-RM tests (chest press, 35.0 ± 3.1 vs. 52.0 ± 3.1, p = 0.002 and leg press, 238.0 ± 7.6 vs. 297.0 ± 5.3, p = 0.001). In addition, BMI (34.2 ± 1.0 vs. 33.7 ± 1.1, p = 0.058), and diastolic BP (77.4 ± 3.0 vs. 70.8 ± 2.4, p = 0.079) tended to be reduced. No significant differences were observed in systolic BP, resting HR, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, or glucose after the RET intervention.

B. Circulating Blood Components

Circulating levels of red and white blood cells, platelets, hemoglobin, hematocrit, and other components of the CBC for OB women at baseline and following a single bout of SWL for all four time points are presented in Table IV. The SWL bout resulted in significant increases in white blood cells at all time points (baseline, 7.0 ± 0.6 vs. 7.9 ± 0.8, p = 0.003; pre-training, 7.0 ± 0.7 vs. 8.1 ± 0.8, p = 0.047; midpoint, 6.8 ± 0.7 vs. 8.0 ± 1.0, p = 0.023; follow-up and 7.0 ± 0.7 vs. 8.0 ± 0.8, p = 0.006) which is indicative of acute inflammation. However, repeated measures analysis demonstrated no significant differences in white blood cells as a result of the RET intervention. In addition, no significant changes were observed in any other components of the CBC as a result of either SWL or RET.

TABLE III

PHYSICAL CHARACTERISTICS, BLOOD PRESSURES, AND METABOLIC RISK FACTORS FOR OBESE WOMEN AT BASELINE AND FOLLOWING 8 WEEKS OF RESISTANCE EXERCISE TRAINING

	Baseline (n=10)	Follow-Up (n=10)	*P* Value
Age (yr)	30.3 ± 1.7	30.3 ± 1.7	1.000
Height (cm)	161.3 ± 2.6	161.3 ± 2.6	1.000
Body Weight (kg)	89.7 ± 4.9	88.8 ± 5.0	0.116
Body mass index ($kg \bullet m^{-2}$)	34.2 ± 1.0	33.7 ± 1.1	0.058
Waist circumference (cm)	95.3 ± 2.3	92.6 ± 2.5*	0.001
Body fat %	42.9 ± 1.3	40.1 ± 1.5*	0.049
Systolic blood pressure (mm Hg)	120.1 ± 2.6	119.5 ± 2.3	0.815
Diastolic blood pressure (mm Hg)	77.4 ± 3.0	70.8 ± 2.4	0.079
Heart rate (beats/min)	70.9 ± 3.6	70.1 ± 3.4	0.790
Daily physical activity (steps/day)	5619.8 ± 204.2	6279.3 ± 150.3*	0.013
Peak VO_2 (ml/kg•min)	31.8 ± 0.9	34.0 ± 0.8*	0.002
Ten-RM Chest (lb)	35.0 ± 3.1	52.0 ± 3.1*	0.002
Ten-RM Leg Press (lb)	238.0 ± 7.6	297.0 ± 5.3*	0.001
Total cholesterol (mg/dL)	195.9 ± 11.3	188.7 ± 11.3	0.450
LDL cholesterol (mg/dL)	113.8 ± 8.2	109.3 ± 8.2	0.524
HDL cholesterol (mg/dL)	56.7 ± 4.0	52.9 ± 2.8	0.081
Triglycerides (mg/dL)	127.3 ± 21.4	111.8 ± 20.5	0.190
Glucose (mg/dL)	85.6 ± 3.0	87.5 ± 3.8	0.356

Peak VO_2, functional capacity; RM, repetition maximum; LDL, low-density lipoprotein; HDL, high-density lipoprotein. Data are presented as mean ± SEM. *Significant difference observed at follow-up versus baseline ($P < 0.05$).

Table IV

CIRCULATING BLOOD COMPONENTS FOR OBESE WOMEN AT FOUR TIME POINTS DURING THE 12-WEEK STUDY PERIOD

	Baseline		**Pre-Training**		**Midpoint**		**Follow-Up**	
	Pre-SWL	**Post-SWL**	**Pre-SWL**	**Post-SWL**	**Pre-SWL**	**Post-SWL**	**Pre-SWL**	**Post-SWL**
WBC (x1000/uL)	7.0 ± 0.6	7.9 ± 0.8*	7.0 ± 0.7	8.1 ± 0.8*	6.8 ± 0.7	8.0 ± 1.0*	7.0 ± 0.7	8.0 ± 0.8*
RBC (xMil/uL)	4.4 ± 0.1	4.4 ± 0.2	4.3 ± 0.1	4.3 ± 0.1	4.3 ± 0.1	4.4 ± 0.1	4.3 ± 0.1	4.3 ± 0.1
HGB (g/dL)	13.5 ± 0.5	13.2 ± 0.5	12.9 ± 0.4	13.0 ± 0.4	13.0 ± 0.4	13.2 ± 0.4	13.0 ± 0.4	13.2 ± 0.4
HCT (%)	39.8 ± 1.5	39.2 ± 1.6	38.2 ± 1.3	38.5 ± 1.3	38.0 ± 0.9	39.0 ± 1.1	38.6 ± 1.0	38.9 ± 1.0
MCV (fL)	89.8 ± 1.6	89.4 ± 1.7	89.8 ± 1.6	89.7 ± 1.7	89.4 ± 1.6	89.6 ± 1.5	90.0 ± 1.5	90.0 ± 1.6
MCH (pg)	30.4 ± 0.6	30.2 ± 0.6	30.4 ± 0.6	30.4 ± 0.6	30.6 ± 0.5	30.5 ± 0.5	30.4 ± 0.6	30.5 ± 0.6
MCHC (g/dL)	33.8 ± 0.2	33.8 ± 0.1	33.8 ± 0.2	33.9 ± 0.1	34.0 ± 0.1	34.0 ± 0.1	33.8 ± 0.2	33.8 ± 0.1
RDW (%)	13.7 ± 0.3	13.7 ± 0.4	14.0 ± 0.5	13.8 ± 0.4	14.0 ± 0.6	14.0 ± 0.5	14.0 ± 0.5	13.8 ± 0.5
PLT (x1000/UL)	285.4 ± 12.3	297.0 ± 15.2	287.8 ± 17.5	295.9 ± 19.2	286.7 ± 16.9	298.5 ± 16.9	289.4 ± 17.2	295.7 ± 19.2
Mean Platelet Volume (fL)	8.8 ± 0.2	8.9 ± 0.2	8.9 ± 0.2	8.9 ± 0.2	9.0 ± 0.1	9.1 ± 0.2	8.9 ± 0.2	8.9 ± 0.2
Neutrophil (%)	58.6 ± 3.0	60.0 ± 3.1	62.3 ± 2.0	61.5 ± 1.9	61.1 ± 2.7	59.2 ± 2.8	61.8 ± 2.0	60.2 ± 2.2
Lymphocyte (%)	33.0 ± 3.0	32.0 ± 3.1	28.6 ± 2.2	29.9 ± 2.0	30.5 ± 2.8	32.3 ± 2.9	29.3 ± 2.2	30.4 ± 2.0
Monocyte (%)	6.3 ± 0.5	5.9 ± 0.6	6.9 ± 0.6	7.2 ± 0.4	6.2 ± 0.4	6.2 ± 0.6	6.7 ± 0.5	7.1 ± 0.4
Eosinophil (%)	1.7 ± 0.3	1.7 ± 0.3	1.8 ± 0.3	1.8 ± 0.3	1.9 ± 0.4	1.8 ± 0.3	1.9 ± 0.3	1.8 ± 0.3
Basophil (%)	0.5 ± 0.1	0.3 ± 0.0	0.3 ± 0.0	0.5 ± 0.1	0.3 ± 0.0	0.5 ± 0.1	0.3 ± 0.0	0.5 ± 0.1

WBC, White blood cells; RBC, Red blood cells; HGB, Hemoglobin; HCT, Hematocrit; MCV, Mean cell volume; MCH, Mean cell hemoglobin; MCHC, Mean corpuscular hemoglobin concentration; RDW, Red blood cell distribution width; PLT, Platelets. Data are presented as mean ± SEM. *Significant difference at $P < 0.05$.

TABLE V

DIETARY PATTERNS FOR OBESE WOMEN AT BASELINE

	n = 10
Energy (kcal/day)	2054.8 ± 325.9
Total fat (g/day)	86.5 ± 18.8
Total carbohydrate (g/day)	238.7 ± 29.6
Total protein (g/day)	80.0 ± 11.9
Vitamin C (mg/day)	137.7 ± 28.3
Vitamin E (mg/day)	9.8 ± 1.5

Data are presented as mean ± SEM. *Significant difference observed at baseline ($P < 0.01$).

C. Vascular Characteristics

Brachial artery characteristics of OB women at baseline and following a single bout of SWL for all four time points are presented in Table VI. Subjects had similar BP and exercise HR responses during each SWL bout (Figures 10 and 11). Repeated measures analysis demonstrated no significant differences in brachial artery diameters before or after SWL at all four time points and FMD was similar before SWL at each time point (baseline, 10.5 ± 0.5; pre-training, 10.6 ± 0.4; midpoint, 11.2 ± 0.8; and follow-up 11.1 ± 0.4). After SWL, FMD was significantly and similarly reduced at baseline and pre-training (8.2 ± 0.5%, $p = 0.002$ and 8.3 ±

0.5%, p = 0.006, respectively) (Figure 12 and Figure 13). When normalized for peak SR, FMD remained significantly reduced at these time points (0.032 ± 0.003 vs. 0.024 ± 0.003, p = 0.008 and 0.032 ± 0.003 vs. 0.025 ± 0.003, p = 0.013, respectively) (Figure 13). The absolute change in brachial artery FMD (before and after SWL) from baseline (-2.3 ± 0.5%) to pre-training (-2.3 ± 0.6%) was not significantly different (Figure 14). At midpoint (after 4 weeks of RET) and follow-up (after 8 weeks of RET), FMD tended to be increased after SWL (12.3 ± 0.9, p = 0.059 and 12.9 ± 1.2, p = 0.106, respectively) and was significantly greater when compared to both baseline and pre-training ($p < 0.001$) (Figure 12 and Figure 13). The absolute change in FMD at midpoint (1.1 ± 0.5%) and follow-up (2.2 ± 0.7%) was also significantly different when compared to baseline and pre-training ($p < 0.001$) (Figure 14). In addition, when normalized for peak SR, the increase in FMD after SWL at follow-up became significant (0.039 ± 0.006 vs. 0.053 ± 0.034; p = 0.020) (Figure 13).

There were no significant differences between peak BFV and peak SR before or after SWL at any time point (Figure 15). In addition, EID dilations to NTG after SWL were similar across all time points (baseline, 21.3 ± 1.2; pre-training, 21.8 ± 1.1; midpoint, 20.5 ± 1.2; and follow-up, 21. 5 ± 0.8) (Figure 16) indicating that RET had no effect on vascular smooth muscle cGMP relaxation mechanisms after acute exertion. Pearson correlations showed no significant relationships between pre- or post-SWL vascular characteristics, physical characteristics, metabolic risk factors, or circulating blood components. However, there was a strong correlation between race and FMD change score at baseline (r = -0.72, p = 0.02), pre-training (r = -0.73, p = 0.03), and follow-up (r = 0.73, p = 0.02). To further investigate this, we ran an additional ANOVA using race as the independent variable and the Bonferroni correction showed statistically significant differences in absolute changes in FMD between White (n= 3) and

Hispanic (n = 2) but not Black (n= 5) OB women at follow-up (Blacks, -2.3 ± 0.6; Whites, -1.9 ± 0.7 vs. Hispanics, -4.5 ± 0.9, p = 0.03). There were also strong trends towards racial differences between Whites and Hispanics at baseline (Blacks, -2.2 ± 0.6; Whites, 0.9 ± 0.7 vs. Hispanics, -4.4 ± 0.9, p = 0.07) and pre-training (Blacks, 3.1 ± 0.7; Whites 0.3 ± 0.8 vs. Hispanics, 4.3 ± 1.0, p = 0.08) (Figure 17).

D. Adipokine and Cytokine Levels

Serum adipokine and cytokine levels for OB women at baseline and following a single bout of SWL for all time points are presented in Table VII. Repeated measures analysis demonstrated no significant differences in serum levels of LEP or ADI after SWL at any time point during the 12-week study period suggesting that the RET intervention had no effect on circulating adipokines in OB women. Serum levels of RES as well as IL-10 were essentially undetectable in OB women before and after SWL at all time points. There were no significant changes in IL-6 or TNF-α as a result of the RET intervention. However, TNF-α tended to be reduced after SWL at baseline (2.09 ± 0.32 vs. 1.34 ± 0.31, p = 0.001) and was significantly increased at follow-up (1.29 ± 0.20 vs. 1.96 ± 0.24, p = 0.065). Pearson correlations demonstrated that these effects were not related to any changes in vascular function, physical characteristics, metabolic risk factors, or circulating blood components at any time point.

Table VI

VASCULAR CHARACTERISTICS FOR OBESE WOMEN AT FOUR TIME POINTS DURING THE 12-WEEK STUDY PERIOD

	Pre-SWL	Post-SWL	*P* Value
Baseline			
Diameter (mm)	3.4 ± 1.2	3.4 ± 1.4	0.447
FMD (%)	10.5 ± 0.5	8.2 ± 0.5*	0.002
Peak BFV (cm/s)	124.8 ± 12.1	134.0 ± 15.8	0.415
FMD peak SR (s-1)	340.5 ± 40.0	370.7 ± 54.7	0.365
Normalized FMD	0.032 ± 0.003	0.024 ± 0.003*	0.008
FMD Δ (%)	(-2.3 ± 0.5)		--
NTG Dilation (%)	ND	21.3 ± 1.2	--
Pre-Training			
Diameter (mm)	3.4 ± 1.3	3.4 ± 1.4	0.375
FMD (%)	10.6 ± 0.4	8.3 ± 0.5*	0.006
Peak BFV (cm/s)	128.5 ± 10.8	130.4 ± 8.8	0.850
FMD peak SR (s-1)	350.9 ± 35.7	363.5 ± 31.8	0.654
Normalized FMD	0.032 ± 0.003	0.025 ± 0.003*	0.013
FMD Δ (%)	(-2.3 ± 0.6)		--
NTG Dilation (%)	ND	21.8 ± 1.1	--
Midpoint			
Diameter (mm)	3.5 ± 1.4	3.5 ± 1.5	0.403
FMD (%)	11.2 ± 0.8	12.3 ± 0.9†	0.059
Peak BFV (cm/s)	112.2 ± 8.7	121.4 ± 9.7	0.395
FMD peak SR (s-1)	289.5 ± 22.9	313.7 ± 30.8	0.432
Normalized FMD	0.040 ± 0.004	0.041 ± 0.005	0.669
FMD Δ (%)	1.1 ± 0.5†		--
NTG Dilation (%)	ND	20.5 ± 1.2	--
Follow-Up			
Diameter (mm)	3.5 ± 1.2	3.1 ± 3.4	0.323
FMD (%)	11.1 ± 0.4	12.9 ± 1.2†	0.106
Peak BFV (cm/s)	121.1 ± 12.1	109.0 ± 11.3	0.186
FMD peak SR (s-1)	317.8 ± 35.6	281.4 ± 32.2	0.144
Normalized FMD	0.039 ± 0.006	0.053 ± 0.034*	0.020
FMD Δ (%)	2.2 ± 0.7†		--
NTG Dilation (%)	ND	21.5 ± 0.8	--

FMD, flow-mediated dilation; FMD Δ, absolute change in FMD; BFV, blood flow velocity; SR, shear rate; EID, endothelium-independent dilation; ND, not determined. Data are presented as mean ± SEM. *Significant difference at $P < 0.05$.

Table VII

SERUM ADIPOKINE AND CYTOKINE LEVELS FOR OBESE WOMEN AT FOUR TIME POINTS DURING THE 12-WEEK STUDY PERIOD

	Pre-SWL	**Post-SWL**	***P* Value**
Baseline			
LEP(ng/mL)	33.2 ± 8.6	68.8± 22.8	0.337
RES (ng/mL)	UD	UD	--
ADI (ng/mL)	6153.3 ± 815.3	4756.9 ± 1398.3	0.378
IL-10 (pg/mL)	UD	UD	--
IL-6 (pg/mL)	4.7 ± 0.8	4.2 ± 0.8	0.777
TNF- α (pg/mL)	2.1 ± 0.3	1.3 ± 0.3	0.065
Pre-Training			
LEP(ng/mL)	42.5 ± 19.2	58.0 ± 24.4	0.280
RES (ng/mL)	UD	UD	--
ADI (ng/mL)	4731.0 ± 923.3	7012.4 ± 1764.0	0.713
IL-10 (pg/mL)	UD	UD	--
IL-6 (pg/mL)	6.1 ± 1.7	7.4 ± 2.1	0.128
TNF- α (pg/mL)	1.7 ± 0.2	2.7 ± 0.9	0.338
Midpoint			
LEP(ng/mL)	22.5 ± 8.6	37.8 ± 19.6	0.187
RES (ng/mL)	UD	UD	--
ADI (ng/mL)	5747.1 ± 1166.6	4538.4 ± 1069.3	0.417
IL-10 (pg/mL)	UD	UD	--
IL-6 (pg/mL)	5.2 ± 1.2	6.7 ± 2.0	0.194
TNF- α (pg/mL)	1.6 ± 0.2	1.6 ± 0.5	0.649
Follow-Up			
LEP(ng/mL)	54.7 ± 17.2	32.5 ± 7.6	0.612
RES (ng/mL)	UD	UD	--
ADI (ng/mL)	4898.0 ± 653.0	6015.3 ± 1089.0	0.566
IL-10 (pg/mL)	UD	UD	--
IL-6 (pg/mL)	3.8 ± 0.7	3.7 ± 0.6	0.777
TNF- α (pg/mL)	1.3 ± 0.2	2.0 ± 0.2	0.001

LEP, leptin; RES, resistin; ADI, adiponectin; IL-10, interleukin-10; IL-6, interleukin-6; TNF-α; tumor necrosis factor-alpha; UD, undetectable. Data are presented as mean ± SEM.
*Significant difference at $P < 0.05$.

Figure 10. Baseline and maximum systolic blood pressure (BP) for individual subjects during a single bout of strenuous weight lifting (SWL) at four time points during the 12-week study period: (A) baseline, (B) pre-training, (C) midpoint, and (D) follow-up. No significant differences observed.

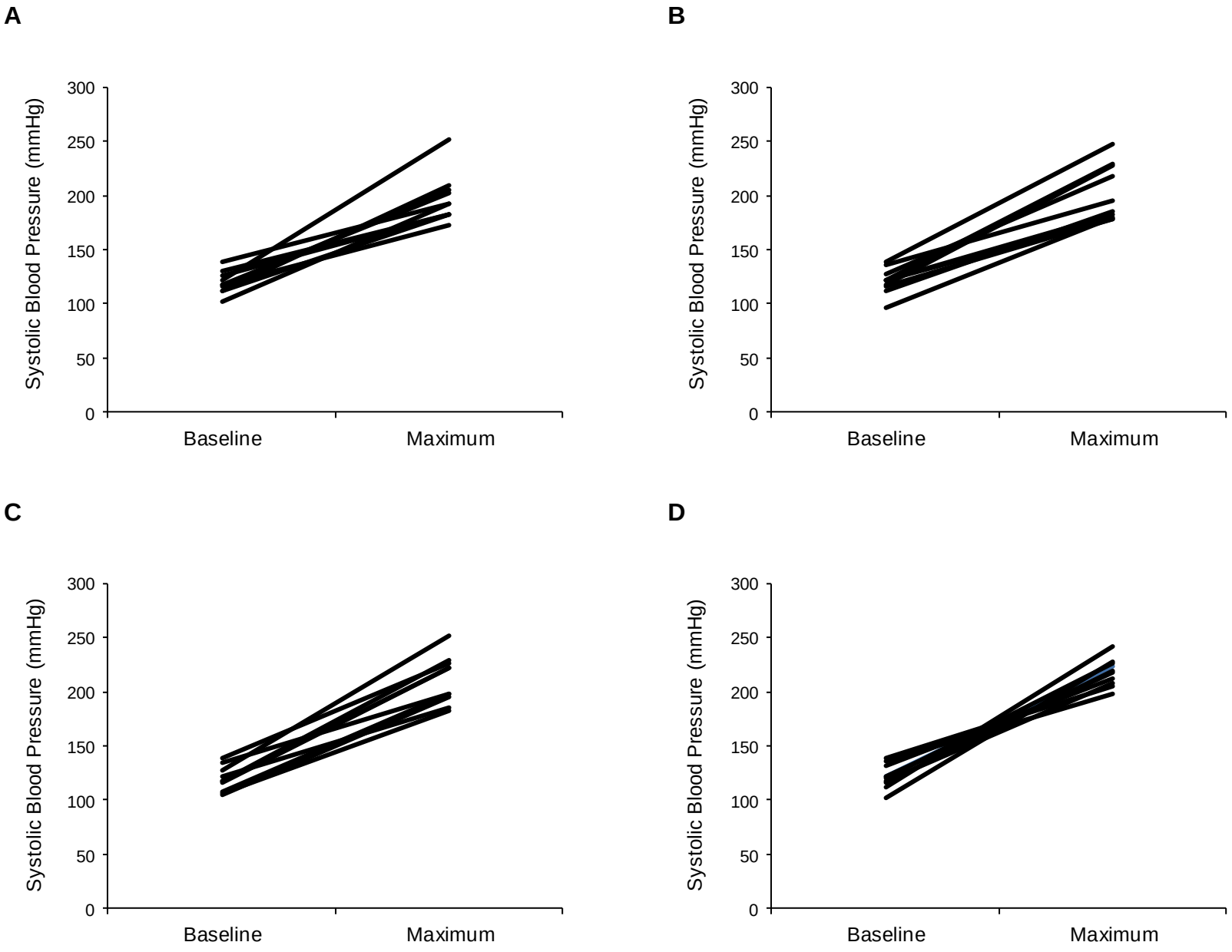

A
B
C
D
Systolic Blood Pressure (mmHg)
300
250
200
150
100
50
0
Baseline
Maximum

Figure 11. Baseline and maximum heart rate (HR) for individual subjects during a single bout of strenuous weight lifting (SWL) at four time points during the 12-week study period: (A) baseline, (B) pre-training, (C) midpoint, and (D) follow-up. No significant differences observed.

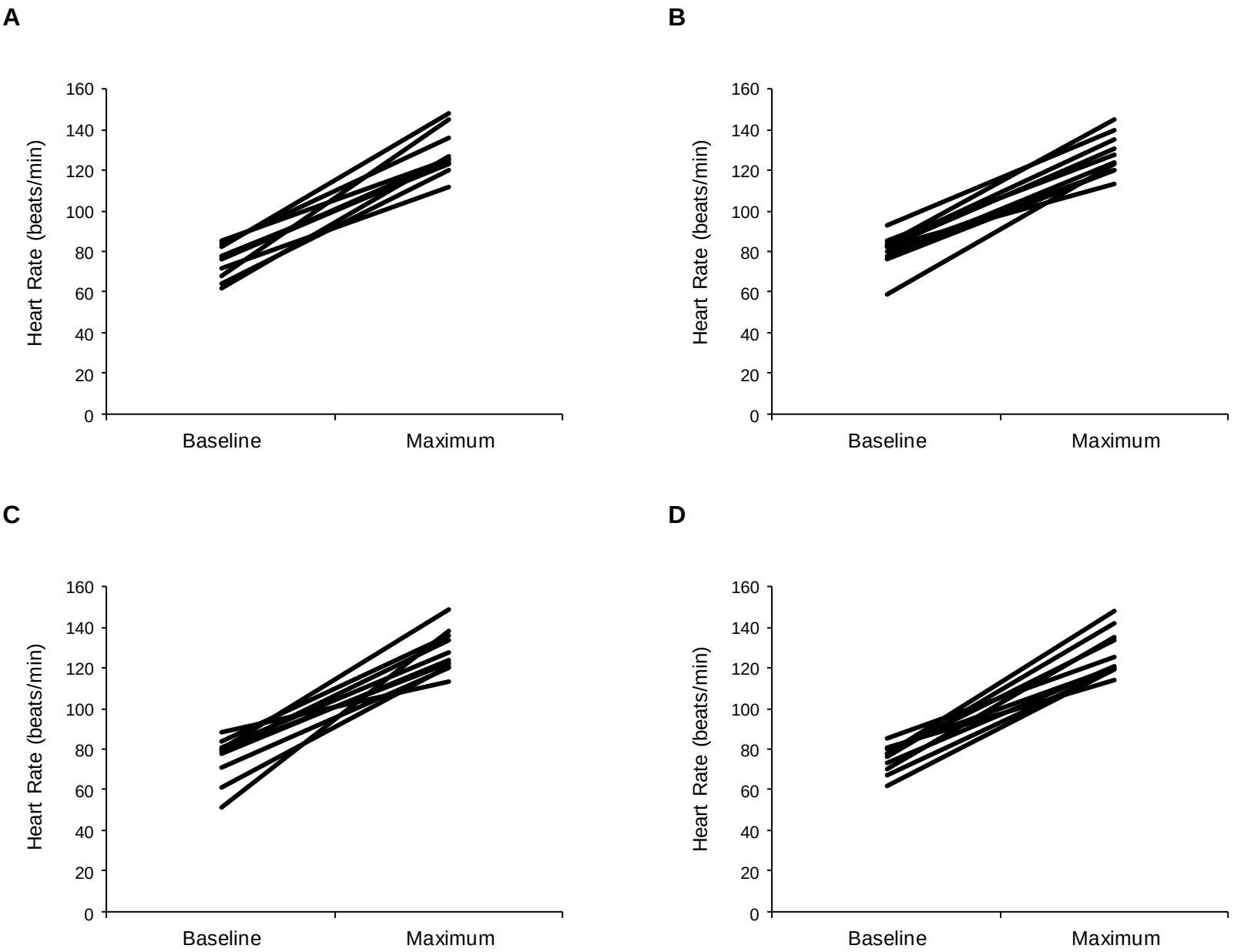
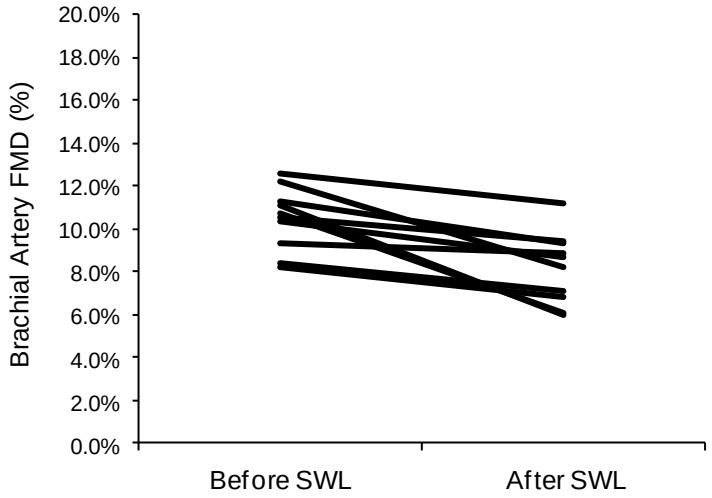
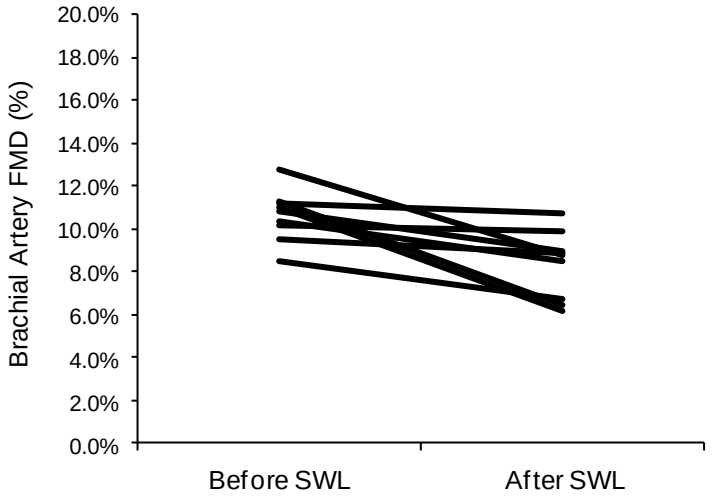

A
B
C
D
Heart Rate (beats/min)
0
20
40
60
80
100
120
140
160
Baseline
Maximum

Figure 12. The effect of a single bout of strenuous weight lifting (SWL) on brachial artery flow-mediated dilation (FMD) at four time points during the 12-week study period: (A) baseline, (B) pre-training, (C) midpoint, and (D) follow-up. Significant differences observed post-SWL versus pre-SWL at baseline and pre-training ($p < 0.01$). Significant differences observed post SWL at midpoint and follow-up versus baseline and pre-training ($p < 0.01$).

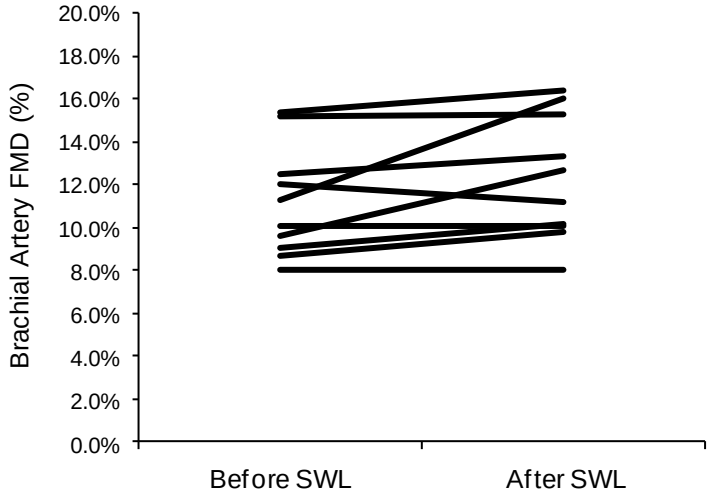
A


Brachial Artery FMD (%)
20.0%
18.0%
16.0%
14.0%
12.0%
10.0%
8.0%
6.0%
4.0%
2.0%
0.0%
Before SWL
After SWL

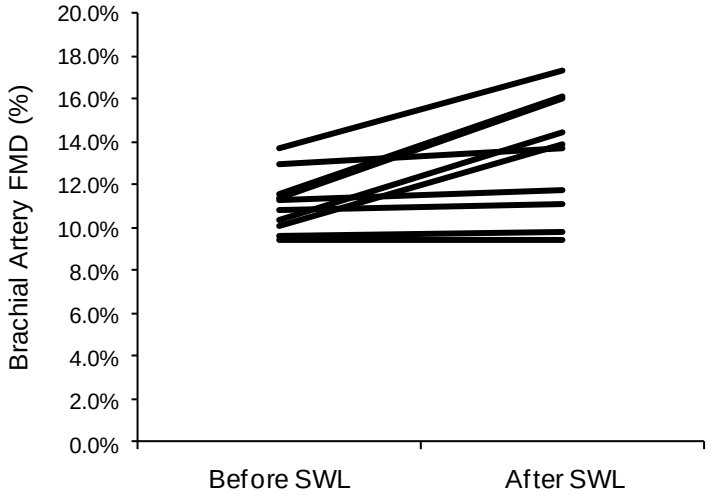
B


Brachial Artery FMD (%)
20.0%
18.0%
16.0%
14.0%
12.0%
10.0%
8.0%
6.0%
4.0%
2.0%
0.0%
Before SWL
After SWL

C


Brachial Artery FMD (%)
20.0%
18.0%
16.0%
14.0%
12.0%
10.0%
8.0%
6.0%
4.0%
2.0%
0.0%
Before SWL
After SWL

D


Brachial Artery FMD (%)
20.0%
18.0%
16.0%
14.0%
12.0%
10.0%
8.0%
6.0%
4.0%
2.0%
0.0%
Before SWL
After SWL

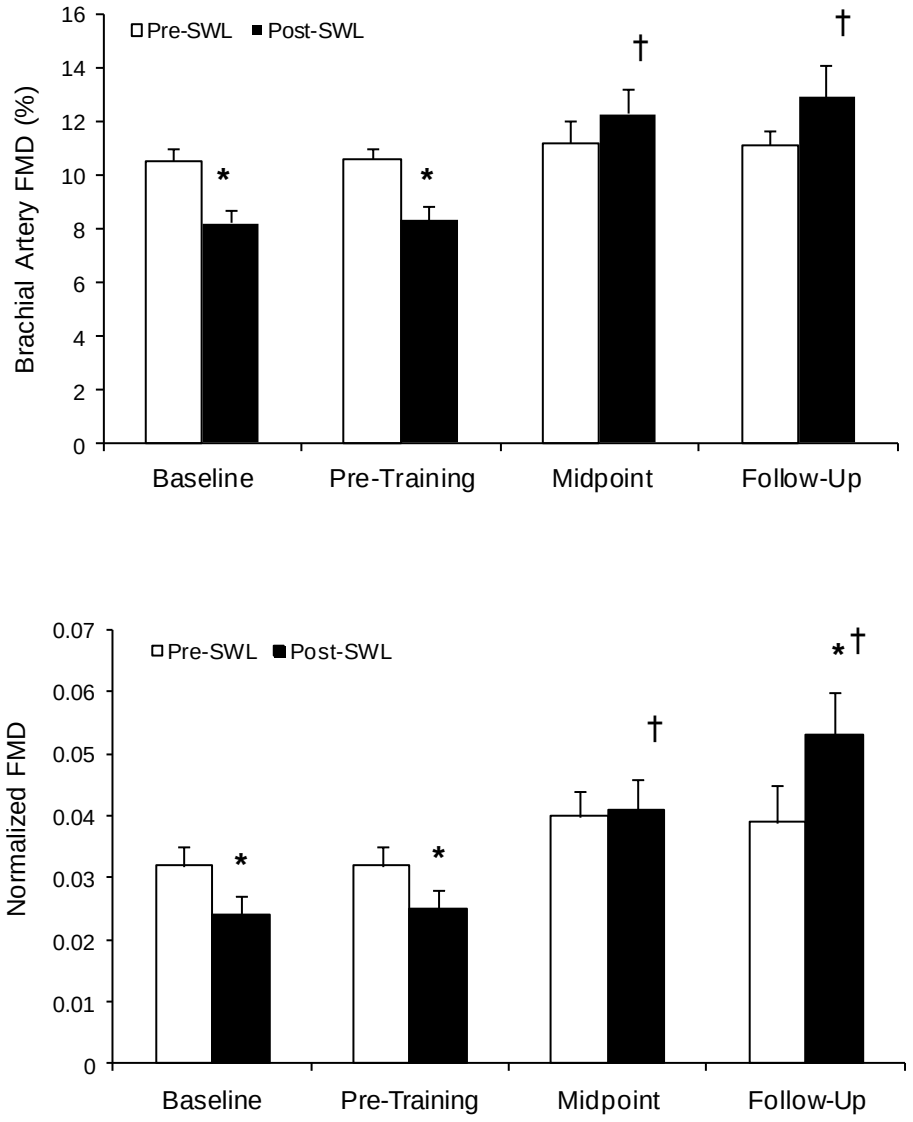


Figure 13. The effect of a single bout of strenuous weight lifting (SWL) on brachial artery flow-mediated dilation (FMD) (top panel) and normalized FMD (bottom panel) in obese sedentary women at four time points during the 12-week study period. *Significant difference observed post-SWL versus pre-SWL ($p < 0.05$). †Significant difference versus Baseline and Pre-Training ($p < 0.05$).

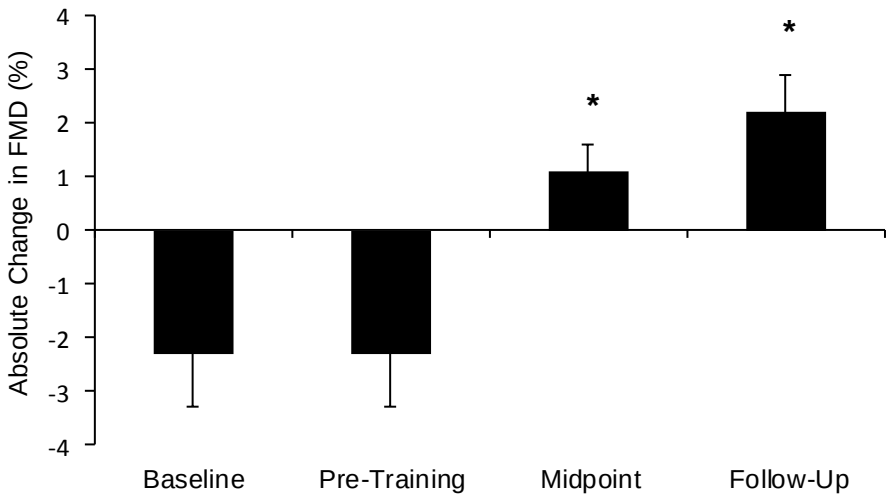


Figure 14. The absolute change in flow-mediated dilation (FMD) in obese sedentary women before and after a single bout of strenuous weight lifting (SWL) at four time points during the 12-week study period. *Significant difference observed versus Baseline and Pre-Training ($p < 0.05$).

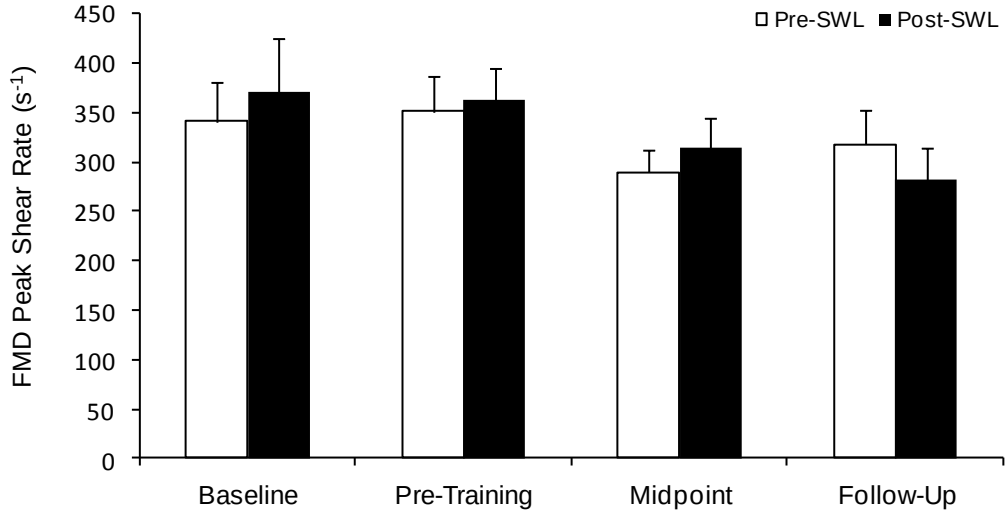


Figure 15. The effect of a single bout of strenuous weight lifting (SWL) on shear rate (SR) during flow-mediated dilation (FMD) in obese sedentary women at four time points during the 12-week study period. No significant differences observed.

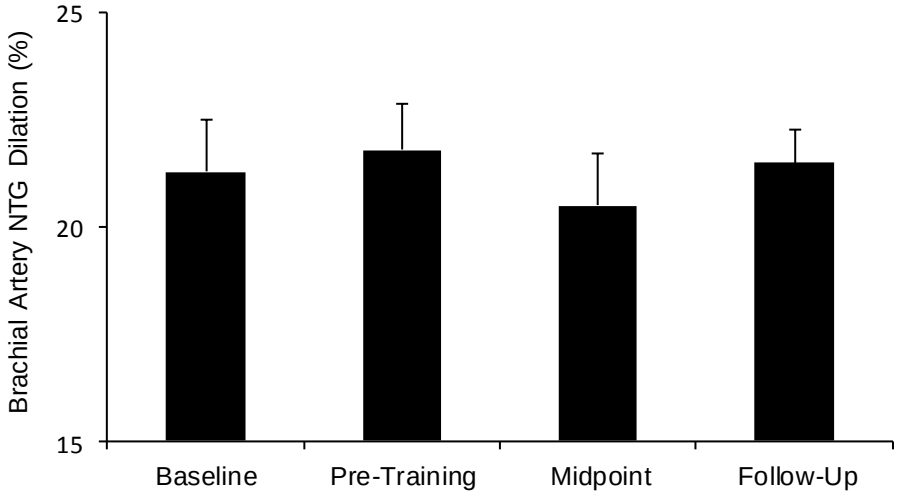


Figure 16. Nitroglycerin (NTG)-induced dilation of the brachial artery in obese (OB) sedentary women after a single bout of strenuous weightlifting (SWL) at four time points during the 12-week study period. No significant differences observed.

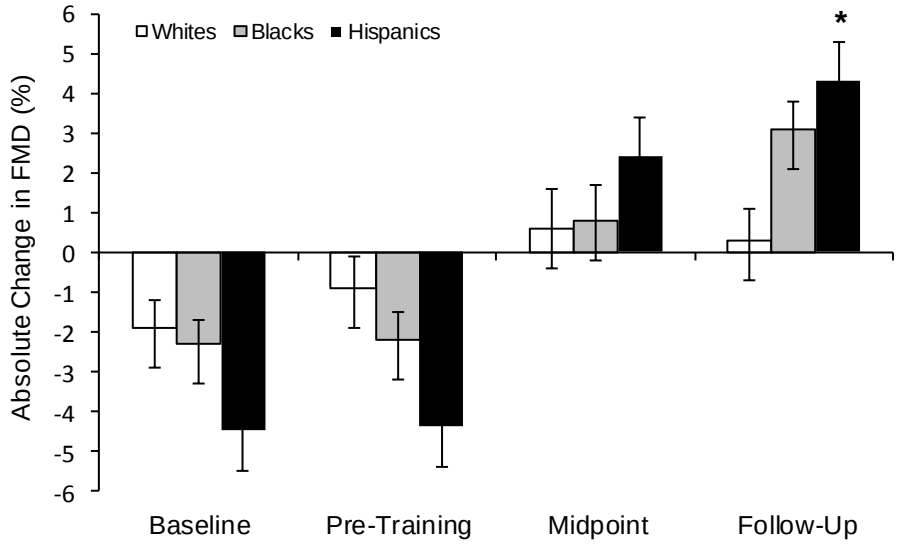


Figure 17. Racial differences in absolute changes in flow-mediated dilation (FMD) among obese sedentary women before and after a single bout of strenuous weight lifting (SWL) at four time points during the 12-week study period. *Significant difference observed between Whites and Hispanics ($p < 0.05$).

V. DISCUSSION

The principle findings of this study include the following: 1) acute exertion during a single bout of strenuous weight lifting impairs flow-mediated dilation of the brachial artery in obese women who are sedentary; 2) an 8-week whole-body, moderate-intensity resistance exercise training intervention enhances flow-mediated dilation after acute exertion and improves waist circumference, body composition, functional capacity, and muscular strength; 3) brachial artery reactivity post-acute exertion is altered after as little as 4 weeks of resistance exercise training; 4) alterations in brachial artery function after resistance exercise training are limited to the endothelium; and 5) brachial artery reactivity post-acute exertion and after 8 weeks of resistance exercise training is not linked to obesity-related changes in adipokine and cytokine production.

A. Effects of Acute Exertion on Nitric Oxide-Mediated Vascular Function in Obesity

Under normal physiologic conditions, NO is the chief vasodilator released by the endothelium and functions in modulating smooth muscle tone and regulating inflammation by preventing leukocyte activation and adhesion (39). In addition, NO prevents atherosclerosis through its anti-proliferative effects on the vascular wall (41). Nitric oxide plays a critical role in vasodilation under conditions of increased blood flow. During increased blood flow, ROS are also produced by eNOS but are usually scavenged by vascular antioxidant enzymes and, subsequently, NO diffuses into adjacent smooth muscle cells and mediates vasodilation (36,49). Impaired vascular function is associated with increased scavenging of NO by elevated ROS (39).

It has previously been shown that acute exertion induces oxidative stress in active as well as sedentary individuals who are unaccustomed to exercise training by enhancing ROS

production, which contributes to a decrease in NO bioavailability and impairs FMD (135,140,141). As exemplified by Quindry and colleagues, an intense bout of aerobic exercise increases blood oxidative stress in young active males as indicated by a decrease in antioxidants (141). In our studies, we have found that a single bout of progressive weightlifting, decreases brachial artery FMD in sedentary lean young men and women. Similar to previous studies of sedentary lean individuals (135), brachial artery FMD after a single bout of SWL was reduced in sedentary obese subjects. Since a sedentary lifestyle is closely linked to obesity (51,99,142) and both are associated with VD and increased risk of CVD (52,98), we expected FMD to be impaired in an obese population of sedentary individuals. Other studies have found impaired FMD responses after acute exercise in sedentary overweight and obese men (143) as well as subjects at risk of CVD (144) but, to our knowledge, this is the first study to determine the effects of acute exertion on FMD responses in obese women.

B. Effects of Resistance Exercise Training on Nitric Oxide-Mediated Vascular Function in Obesity

Although acute exertion has been shown to impair vascular function through increased ROS generation and oxidative stress, repetitive increases in blood flow during regular exercise training have been shown to improve vascular function as assessed by FMD (106,108). In addition, human and animal studies implementing various exercise models have shown increases in eNOS activity as well as reductions in oxidative stress as a result of training (109,145). For example, 4 weeks of aerobic exercise training has been shown to improve acetylcholine-mediated endothelium-dependent vasodilation and this effect was closely linked to changes in eNOS expression (145). Likewise, resistance exercise training was shown to improve age-associated vascular dysfunction in conduit arteries of rats through regulation of eNOS activity

(109). There is a plethora of research demonstrating that aerobic exercise training enhances vascular function in overweight and obese adults (20,146,147), however, few studies have investigated the vascular effects of resistance exercise training alone. For this study, we implemented a resistance exercise training intervention using progressive resistance over a period of 8 weeks. This intervention was designed in accordance with recommendations outlined by the ACSM (138).

To our knowledge, this is the first study to determine the effects of resistance exercise training on brachial artery reactivity after acute exertion in the presence of obesity. We found that an 8-week RET intervention improves FMD after acute exertion in sedentary obese women. Although speculative, it is likely that the mechanism of improvement is, in part, a result of an adaptive response occurring within the vascular wall as a result of repeated episodic increases in shear stress during resistance exercise training.

Others have found RET interventions to have vascular protective effects in sedentary overweight and obese populations (106,148) but such effects have not been demonstrated after acute exertion which is known to impair vascular function. Using a 1-year intervention, Olson and colleagues provided the initial demonstration that resistance exercise training alone improves brachial artery FMD in overweight women independent of changes in BP, fasting lipids, and glucose (106). Significant improvements in body composition and muscular strength were also demonstrated in overweight women after 1 year of resistance exercise training. It is worth noting that, overweight women in this study demonstrated markedly reduced FMD responses before and after RET (less than 7.0 and 9.0, respectively) compared to the obese women in our studies (Table VI). Obesity induces increases in total blood volume and mean blood flow which is, in part, caused by an increase in metabolic demand induced by excess body weight (149,150). This

increase in metabolic demand may greatly enhance vasodilator capacity in obese individuals; therefore, it is likely that FMD responses to any given stimuli will be greater in obese individuals compared to those who are overweight or lean. Compensatory vasodilators (i.e. prostaglandins) may have also contributed to this response (151), but this needs to be further elucidated. Vasodilator prostaglandins have previously been shown to play a pivotal role in the regulation of vascular tone at rest and during changes in physiologic demand (i.e. reactive and exercise hyperemia) in the presence of atherosclerosis and CVD risk factor (151). Indeed, our pilot studies showed increased brachial artery FMD in sedentary obese but otherwise healthy subjects before and after acute exertion compared to lean subjects (Table II).

Although our studies involved obese adults, RET has also been shown to improve vascular function in obese adolescents. In a study performed by Watts and colleagues an intervention implementing resistance-based circuit training was shown to normalize brachial artery FMD with concomitant improvements in functional capacity, muscular strength, and body composition (148). Blood pressure and fasting levels of lipids and glucose were unaltered by the intervention. Similar to our studies, an 8 week intervention was implemented. However, we also evaluated changes in brachial artery reactivity after 4 weeks of RET which provided some additional insight regarding the effects of resistance exercise on vascular function overtime. There is evidence that several weeks of exercise training associated with repeated exposure to shear stress may stimulate increased production of NO through improvements in eNOS expression (22). Indeed, we found that brachial artery FMD after acute exertion was significantly increased after only 4 weeks of RET which is indicative of enhanced NO production.

Consistent with the aforementioned studies and some carried out by others using AET (106,146,148) there were no resistance exercise-associated changes in BP, fasting total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, or glucose in obese women after an 8-week RET intervention suggesting that the effects of longer RET interventions may not be mediated by alterations in CVD risk factors. Furthermore, vasodilator responses to NTG after SWL were unaltered after RET thereby ruling out alterations in vascular smooth muscle function as a result of the intervention. Resistance exercise training may enhance vascular function independently through direct mechanical effects of recurrent wall shear stress on NO production (152,153). Several studies report that exercise training enhances shear stress which stimulates NO production and upregulates eNOS expression (109,154,155). These data suggest that improvements in brachial artery FMD after RET in obesity may result from enhanced NO bioavailability. Furthermore, improvements in brachial artery reactivity after a single bout of SWL are likely due to adaptations to recurring shear stress associated with repeated bouts of resistance exercise as a result of training.

C. Effects of Acute Exertion and Resistance Exercise Training on Serum Adipokines and Cytokines in Obesity

Contrary to our hypothesis, no significant changes were observed in serum adipokine or cytokine levels as a result of either the single bout of SWL or the RET intervention. In humans, acute aerobic and resistance exercise are associated with VD and inflammation involving increased production of pro-inflammatory cytokines (140,156,157). Studies have linked the inflammatory response to exertion-induced muscle injury as a result of unaccustomed or strenuous exercise involving high-force and/or repetitive eccentric contractions such as resistance exercise, cycling, and downhill running (140,158). The local inflammatory response

to muscle injury is characterized by immediate leukocyte infiltration with neutrophils representing 50 to 60% of the total circulating pool (159,160). Neutrophilic generation of ROS can contribute to systemic inflammation, oxidative stress, and VD after muscle injury (161,162). Given that obesity is associated with low-grade inflammation characterized by dysregulation of adipokine production (29), enhanced ROS production, and reduced NO bioavailability (12,31) it is plausible to hypothesize that VD and inflammation after acute exertion is augmented in an obese population.

We expected alterations in brachial artery FMD after acute exertion and RET to be associated with changes in serum adipokine and cytokine levels in obese women. However, RES and IL-10 levels were virtually undetectable before and after SWL at all time points and there were no significant changes in LEP, ADI, or IL-6. Serum levels of TNF-α were significantly different after SWL at follow-up but these changes were not associated with alterations in FMD. Interestingly, there were significant elevations in WBCs after SWL at all time points (Table IV) indicating the presence of an inflammatory response, however, these increases were not related to vascular function.

Acute bouts of aerobic and resistance exercise have been shown to increase circulating levels of TNF-α and IL-6 in healthy humans (157,159,160). However, several studies have reported that the time-course for increases in these cytokines varies among different models of acute exertion with some reporting peak increases at 1 hour, 24 hours, and 72 hours post-exercise (157,163,164). We obtained a single blood sample for measurement of each cytokine within 90 minutes of SWL and, therefore, we could not examine specific effects of inflammation on vascular function over a set time-course. As such, the specific role of pro-inflammatory

cytokines in vascular function needs to be further investigated through repeated measures over a time-course of at least 72 hours.

Reduced circulating levels of LEP and RES and increased levels of ADI have been found in individuals who regularly participate in exercise training compared to those who are sedentary (124,165). Research investigating various forms of exercise training on obesity-related changes in adipokine profiles suggest that a combination of AET and RET is required for beneficial modulation of adipokines in obesity (165). Other studies report that a minimum amount of weight loss is required for significant improvements in circulating levels of LEP, RES, and ADI (166,167). This study involved the performance of RET alone and although significant changes in body composition were observed in obese women, no substantial amount of weight loss occurred. Studies examining the interactive effects of RET, AET, and diet on vascular function and adipokine profiles in obesity are definitely warranted.

D. Limitations and Future Studies

There are some limitations of this study. First, the generalizability of the study is a limiting factor given that there were only 10 subjects included and all were women. However, implementation of a within-subjects, repeated measures design allowed us to carefully control experimental variability with a small sample size. Future studies with larger sample sizes are necessary to validate our findings. In addition, inclusion of sedentary obese men in future studies will help to determine the possible gender specific influences of exercise training on NO-mediated endothelium-dependent vasodilator responses to acute exertion. Also, a fully controlled parallel-groups design needs to be implemented in future studies in order to determine specific effects of various types of exercise training (i.e. AET vs. RET, or both) on acute exertion-induced vascular responses. Second, since we only obtained blood samples within 90

minutes after acute exertion at each time point we cannot conclusively state that alterations in serum adipokine and cytokine levels did not play a role in vascular responses to acute exertion and RET. Future studies should assess changes in vascular function and serum adipokines and cytokines over a set time-course in order to examine the specific role of inflammation in VD after acute exertion. Third, we did not assess for any circulating markers of oxidative stress (i.e. malondialdehyde, MDA), therefore, the specific role of ROS in acute exertion-induced impairment of vascular function cannot be fully elucidated. Although brachial artery FMD is a NO-mediated response and impairments in FMD are likely due to reductions in NO bioavailability, further studies should include oxidative stress assay measurements (i.e. (thiobarbituric acid reactive substances assay, TBARS) (68). Fourth, CVD risk factors including BP and LDL cholesterol levels were slightly elevated in some OB subjects which may have influenced vascular function after acute exertion. However, in our analysis there were no significant changes in CVD risk factors and no associations with brachial artery FMD were revealed. Fifth, although the degree of change in brachial artery reactivity post-acute exertion after 8-weeks of RET appears to be related to race, our small sample size makes it difficult to draw any definitive conclusions. However, there is a need for future studies with larger sample sizes to examine the impact of race on vascular responses to acute exertion and exercise training as racial disparities in CVD risk may be related, in part, to race-associated differences in VD (168,169). Finally, our results may have been confounded by nutritional status due to potential differences in total calories as well as macronutrient and micronutrient consumption among obese subjects. All subjects were required to complete a brief food frequency questionnaire prior to participation. However, self-reported dietary intake is often underestimated (170), therefore,

the influence of nutritional differences between OB subjects still needs to be addressed in future studies of vascular function.

E. Clinical Relevance of the Study Results

Although the study participants were all young women, we were able to ascertain novel and clinically relevant information. Atherosclerotic CVD is the third leading cause of preventable death among women between the ages of 25 and 44 years (171). However, CVD is often asymptomatic in women (171) which makes early detection difficult. Obesity and sedentary lifestyle are interrelated epidemics that independently contribute to increased risk of CVD in women (172) making them important therapeutic targets for prevention. We have found that FMD is impaired in sedentary obese, but otherwise healthy young women after acute exertion and that this impairment is amendable to resistance exercise training. Since FMD correlates well with coronary artery function (6) the results of our studies may extend to reduce and even predict CVD risk among women since 1) exercise training attenuates vascular dysfunction through its beneficial effects on conduit artery function (106,108), and 2) acute exertion can trigger acute myocardial infarction in individuals who are sedentary (173). The latter is especially important since women have increased morbidity and mortality rates after myocardial infarction compared to men (174). Given that the burden of CVD is increasing in women yet they are significantly underrepresented in CVD-related research trials (175), the results of this study contribute to a better understanding of the mechanisms by which exercise training promotes vascular health in women.

F. Conclusions

In conclusion, the results of this study suggest that acute exertion impairs NO-mediated endothelium-dependent vasodilation in obese adults who are sedentary and these effects are independent of systemic inflammation associated with alterations in serum adipokine and cytokine levels. Furthermore, acute exertion-induced impairment of vascular function in obese adults is reversible with resistance exercise training. These findings may be important in understanding the link between obesity and vascular dysfunction and may have implications for designing safe exercise training programs for individuals at risk of atherosclerotic CVD. In addition, these findings may have important implications for how vascular and hemodynamic responses to other acute physiological perturbations such as acute hypertension, systemic hypoxemia, and hyperglycemia are altered during obesity.

G. Final Remarks

There appears to be a general theme in the study of exercise—Humans are designed to be physically active and that not doing so creates imbalances within the body that ultimately contribute to obesity and other health problems. As evidence, over 500,000 people die each year from diseases linked to physical inactivity and obesity. Furthermore, rates of hypertension, hypercholesterolemia, type 2 diabetes, and certain forms of cancer have all tripled over the past 30 years corresponding to decreasing levels of daily physical activity and increasing rates of obesity.

In the not so distant past, human beings were required to perform strenuous physical activity daily as they had to hunt and gather food and constantly roam for shelter. In addition, since food supplies were scarce and unpredictable, it was nearly impossible to overc nsume on a daily basis. As late as the early 1900s, physical activity was inevitable since many jobs required

manual labor and owning an automobile was not the norm. Nowadays, we step into our high-powered vehicles and drive to the nearest donut shop for a quick breakfast and a long day in front of a computer.

While modern times have improved human efficiency and productivity, many of today's technological advances support inactive behaviors. People are living longer when compared to hunters and gatherers of the past; however, they are considerably unhealthier. Although people are no longer required to hunt and gather for survival, this type of lifestyle is embedded in our genetic code. As such, there is a need to create an environment that promotes regular physical activity and good nutrition in order to maintain a healthy lifestyle.

There are many reasons why the results of this study are important, especially for women. As has been emphasized throughout this thesis, CVD is a leading cause of preventable death among young women. Unfortunately, there are often no symptoms of CVD in these women which makes early detection and prevention quite difficult. Obesity and a lack of physical activity irrefutably contribute to increased risk in women. Even when women are moderately overweight, their risk of disease is increased.

A major finding of this study is that arterial function is compromised in young sedentary obese women when their cardiovascular system is taxed with strenuous exertion. Given that the average screening exam for CVD does not include an evaluation of arterial function during exertion, this is clinically important as it is a potential explanation as to why CVD may go undetected for significant periods of time in young adults. The good news is that we have also shown that the impairment in arterial function can be reversed with habitual resistance exercise training. This finding suggests that regular taxing of the cardiovascular system with exercise is beneficial and supports the premise that human beings are designed to be physically active.

For future studies I will focus on the specific role of regular physical activity on various aspects of oxidative stress and inflammation related to obesity, hypercholesterolemia, hypertension, and type 2 diabetes, as well as mechanisms by which the cardiovascular system is affected. In the longer term, my studies will be aimed at promoting health through initiation of community-based prevention and intervention research with programs that provide exercise prescription and programming as well as lifestyle, nutrition, and weight management services based on sound scientific principles.

APPENDICES

Appendix A

Recruitment Advertisement

HEALTHY, OBESE PARTICIPANTS NEEDED FOR AN EXERCISE STUDY

The effects of resistance training on vascular health – Researchers from the University of Illinois at Chicago are performing a clinical research study on the effects of resistance training on the function of blood vessels of the cardiovascular system. Total participation in the research study will last 4-5 months and include health screenings and assessments, ultrasound evaluations, and body fat analyses. In addition, subjects will be asked to provide fluid and tissue samples. Participants will undergo these procedures in the Clinical Research Center at the University of Illinois.

Researchers are seeking adults between the ages of 18 and 55 for participation. Qualified participants will receive monetary compensation as well as free body fat analyses, complete health screenings, and personal training services.

For more information about participation in this study, please contact Nina Franklin at (312) 996-3574 or Shane Phillips/Melissa Goslawski at (312) 413-5265. Please mention that you are calling in reference to the RT Study.

Appendix B

Resistance Training and Vascular Dysfunction
Medical and Exercise History Questionnaire

1. Age: _____ Gender: Male Female Race: White/Caucasian
   Height: _____ Black/African-American
   Weight: _____ Hispanic/Latino
   Asian/Pacific Islander
   Native American
   Other: _____

2. Cardiovascular Risk Factors:

   A. Do you have a family history of heart attack, bypass surgery, or stroke?

      Yes No

   B. Have you ever had a heart attack or do you experience chest pain? Yes No

   C. Do you smoke or use tobacco? Yes No

   D. Describe your blood pressure:

      High Borderline Normal Low Not Sure

   E. Do you have diabetes? Yes No

   F. Do you have high cholesterol? Yes No

   G. How much do you experience stress? Frequently Sometimes Never

3. Do you have anemia? Yes No

4. Have you ever had a knee, hip, or leg injury that prevented you from performing lower body leg exercise? Yes No

5. Have you ever had surgery? Yes No If yes, describe:
   _____
   _____

6. How would you describe your exercise routine?

   A. The number of days I usually lift weights is:

0 1 2 3 4 5 6 7

B. The number of days per week I do at least 30 minutes of aerobic exercise (walking, running, swimming, rowing, etc.) is:

0 1 2 3 4 5 6 7

C. The number of months I have been lifting weights is:

3 or less 6 or less 9 or less 12 or less more than 12

D. The number of months I have performed aerobic exercise is:

3 or less 6 or less 9 or less 12 or less more than 12

7. Have you been diagnosed with an eating disorder? Yes No

8. Are you currently taking any medications? If so, describe:

_____

_____

9. Are you currently taking any vitamin or health supplements or performance enhancers, including steroids? If so, describe:
10. Do you take any vitamin supplements or a daily vitamin (Vitamins B, C, E, Mg, Ca, Folate)? If so, describe:

_____

_____

11. Do you drink a glass of purple grape juice or red wine per day? Yes No

12. Have you exercised in the past 24 hours? If so, describe the exercise routine:

_____

_____

Appendix C

Pedometer Log (Sample)

Pedometer Log Sheet

Participant ID: XXXXXX
Participant Initials: XX

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Day 1	4589	5693	4965	5987	5963	5947	5312	5648	7894	5200	4649	6657
Day 2	7896	8542	8056	8167	7562	8125	9547	9681	8899	9476	8630	6446
Day 3	7756	9485	7643	8723	8495	7432	9611	7453	6320	9301	4549	9561
Day 4	8900	7128	9132	9485	7365	6438	9784	8086	6630	7023	6903	6167
Day 5	7963	9564	5468	8236	9521	8956	9548	7302	8014	7025	7564	5152
Day 6	7630	8432	7489	7956	9648	9865	8456	8647	9966	9548	8643	6465
Day 7	5562	5523	5896	8795	8465	5528	9205	8520	6564	8652	6598	9582
Weekly Average	7185.143	7766.714	6949.857	8192.714	8145.571	7470.143	8780.429	7905.286	7755.286	8032.143	6790.857	7147.143

Overall Average	7676.774

Appendix D

Ten-Repetition Maximum Tests (Sample)

UPPER-BODY TESTS					
Exercise	**Trial #1** Weight / Reps	**Trial #2** Weight / Reps	**Trial #3** Weight / Reps	**10-RM Weight**	**Notes**
Vertical Chest Press (Machine)	30 / 12	41 / 10		**10**	
Mid Row (Machine)	60 / 16	75 / 10		**75**	
Lat Pulldown (Machine)	38 / 20	50 / 15	62 / 10	**62**	
Shoulder Press (Machine)	21 / 13	30 / 10		**10**	
LOWER-BODY TESTS					
Exercise	**Trial #1** Weight / Reps	**Trial #2** Weight / Reps	**Trial #3** Weight / Reps	**10-RM Weight**	**Notes**
Leg Press (Machine)	266 / 13	292 / 12	318 / 10	**318**	
Toe Raise (Machine)	266 / 20	292 / 16	318 / 10	**318**	
Leg Extension (Machine)	44 / 13	51 / 12	57 / 10	**57**	
Leg Curl (Machine)	75 / 15	86 / 10		**86**	

Appendix E

Training Log (Sample)

DATE / DAY: XXXXX	**WARM-UP:** Stationary Bike			
EXERCISE	**WEIGHT (in lb.) / REPETITIONS**			**NOTES**
Squat (Dumbbells)	15 / 8	15 / 10	15 / 8	
Vertical Chest Press (Machine)	30 / 12	30 / 10	41 / 8	
Mid Row (Machine)	60 / 10	60 / 10	60 / 8	
Shoulder Press (Machine)	30 / 10	30 / 8	30 / 10	
Seated Leg Curl (Machine)	86 / 10	86 / 12	86 / 10	
Triceps Pushdown (Machine)	12 / 10	12 / 8	12 / 8	
Biceps Curl (Dumbbells)	8 / 10	8 / 10	10 / 8	
Lateral Raise (Dumbbells)	8 / 8	8 / 12	8 / 9	
Leg Extension (Machine)	44 / 8	44 / 10	44 / 7	

DATE / DAY: XXXXX	**WARM-UP:** Stationary Bike			
EXERCISE	**WEIGHT (in lb.) / REPETITIONS**			**NOTES**
Seated Leg Press (Machine)	292 / 10	292 / 12	292 / 10	
Seated Row (Machine)	12 / 10	12 / 12	15 / 8	
Incline Bench Press (Dumbbells)	12 / 8	12 / 8	12 / 9	
Lunge (Dumbbells)	8 / 10	8 / 8	8 / 10	
Upright Row (Dumbbells)	8 / 8	8 / 8	8 / 9	
Dumbbell Fly	8 / 10	8 / 12	8 / 12	
Calf Raise (Machine)	292 / 12	292 / 13	318 / 10	
Front Raise (Dumbbells)	8 / 8	8 / 9	8 / 9	
Cable Biceps Curl (Machine)	12 / 8	12 / 8	12 / 8	
Triceps Kickback (Dumbbells)	8 / 10	8 / 10	15 / 8	

CITED LITERATURE

1. Pleis JR, Ward BW, Lucas JW. Summary health statistics for U.S. adults: National Health Interview Survey, 2009. Vital Health Stat.10 2010 Dec;(249):1-207.

2. Li TY, Rana JS, Manson JE, Willett WC, Stampfer MJ, Colditz GA, Rexrode KM, Hu FB. Obesity as compared with physical activity in predicting risk of coronary heart disease in women. Circulation 2006 Jan 31;113(4):499-506.

3. Hwu CM, Hsiao CF, Kuo SW, Wu KD, Ting CT, Quertermous T, Rodriguez B, Chen I, Grove J, Chen PY, et al. Physical inactivity is an important lifestyle determinant of insulin resistance in hypertensive patients. Blood Press 2004;13(6):355-61.

4. Prasad DS, Das BC. Physical inactivity: a cardiovascular risk factor. Indian J.Med.Sci. 2009 Jan;63(1):33-42.

5. Celermajer DS, Sorensen KE, Bull C, Robinson J, Deanfield JE. Endothelium-dependent dilation in the systemic arteries of asymptomatic subjects relates to coronary risk factors and their interaction. J.Am.Coll.Cardiol. 1994 Nov 15;24(6):1468-74.

6. Hashimoto M, Kozaki K, Eto M, Akishita M, Ako J, Iijima K, Kim S, Toba K, Yoshizumi M, Ouchi Y. Association of coronary risk factors and endothelium-dependent flow-mediated dilatation of the brachial artery. Hypertens.Res. 2000 May;23(3):233-8.

7. Suvorava T, Lauer N, Kojda G. Physical inactivity causes endothelial dysfunction in healthy young mice. J.Am.Coll.Cardiol. 2004 Sep 15;44(6):1320-7.

8. Hamburg NM, McMackin CJ, Huang AL, Shenouda SM, Widlansky ME, Schulz E, Gokce N, Ruderman NB, Keaney JF, Jr., Vita JA. Physical inactivity rapidly induces insulin resistance and microvascular dysfunction in healthy volunteers. Arterioscler.Thromb.Vasc.Biol. 2007 Dec;27(12):2650-6.

9. Laufs U, Wassmann S, Czech T, Munzel T, Eisenhauer M, Bohm M, Nickenig G. Physical inactivity increases oxidative stress, endothelial dysfunction, and atherosclerosis. Arterioscler.Thromb.Vasc.Biol. 2005 Apr;25(4):809-14.

10. Anfossi G, Russo I, Doronzo G, Pomero A, Trovati M. Adipocytokines in atherothrombosis: focus on platelets and vascular smooth muscle cells. Mediators.Inflamm. 2010;2010:174341.

11. Zhang C. The role of inflammatory cytokines in endothelial dysfunction. Basic Res.Cardiol. 2008 Sep;103(5):398-406.

12. Chudek J, Wiecek A. Adipose tissue, inflammation and endothelial dysfunction. Pharmacol.Rep. 2006;58 Suppl:81-8.

13. Kelley GA, Kelley KS. Efficacy of aerobic exercise on coronary heart disease risk factors. Prev.Cardiol. 2008;11(2):71-5.

14. Tresierras MA, Balady GJ. Resistance training in the treatment of diabetes and obesity: mechanisms and outcomes. J.Cardiopulm.Rehabil.Prev. 2009 Mar;29(2):67-75.

15. Shaw BS, Shaw I. Effect of resistance training on cardiorespiratory endurance and coronary artery disease risk. Cardiovasc.J.S.Afr. 2005 Sep;16(5):256-9.

16. Hodges GJ, Sharp L, Stephenson C, Patwala AY, George KP, Goldspink DF, Tim CN. The effect of 48 weeks of aerobic exercise training on cutaneous vasodilator function in post-menopausal females. Eur.J.Appl.Physiol 2010 Apr;108(6):1259-67.

17. Miyaki A, Maeda S, Yoshizawa M, Misono M, Saito Y, Sasai H, Kim MK, Nakata Y, Tanaka K, Ajisaka R. Effect of habitual aerobic exercise on body weight and arterial function in overweight and obese men. Am.J.Cardiol. 2009 Sep 15;104(6):823-8.

18. Xiang GD, Pu J, Sun H, Zhao L, Yue L, Hou J. Regular aerobic exercise training improves endothelium-dependent arterial dilation in patients with subclinical hypothyroidism. Eur.J.Endocrinol. 2009 Nov;161(5):755-61.

19. Heylen E, Mansourati J, Thioub S, Saiag B, Guerrero F. Effect of exercise training on cutaneous microcirculation in rats. J.Sports Med.Phys.Fitness 2008 Jun;48(2):246-51.

20. Higashi Y, Sasaki S, Kurisu S, Yoshimizu A, Sasaki N, Matsuura H, Kajiyama G, Oshima T. Regular aerobic exercise augments endothelium-dependent vascular relaxation in normotensive as well as hypertensive subjects: role of endothelium-derived nitric oxide. Circulation 1999 Sep 14;100(11):1194-202.

21. Green DJ, Carter HH, FitzSimons MG, Cable NT, Thijssen DH, Naylor LH. Obligatory role of hyperaemia and shear stress in microvascular adaptation to repeated heating in humans. J.Physiol 2010 May 1;588(Pt 9):1571-7.

22. Green DJ, Maiorana A, O'Driscoll G, Taylor R. Effect of exercise training on endothelium-derived nitric oxide function in humans. J.Physiol 2004 Nov 15;561(Pt 1):1-25.

23. Heffernan KS, Fahs CA, Iwamoto GA, Jae SY, Wilund KR, Woods JA, Fernhall B. Resistance exercise training reduces central blood pressure and improves microvascular function in African American and white men. Atherosclerosis 2009 Nov;207(1):220-6.

24. Tinken TM, Thijssen DH, Hopkins N, Black MA, Dawson EA, Minson CT, Newcomer SC, Laughlin MH, Cable NT, Green DJ. Impact of shear rate modulation on vascular function in humans. Hypertension 2009 Aug;54(2):278-85.

25. Quyyumi AA, Patel RS. Endothelial dysfunction and hypertension: cause or effect? Hypertension 2010 May;55(5):1092-4.

26. Jurva JW, Phillips SA, Syed AQ, Syed AY, Pitt S, Weaver A, Gutterman DD. The effect of exertional hypertension evoked by weight lifting on vascular endothelial function. J.Am.Coll.Cardiol. 2006 Aug 1;48(3):588-9.

27. Olson TP, Schmitz KH, Leon AS, Dengel DR. Vascular structure and function in women: relationship with body mass index. Am.J.Prev.Med. 2006 Jun;30(6):487-92.

28. Schjerve IE, Tyldum GA, Tjonna AE, Stolen T, Loennechen JP, Hansen HE, Haram PM, Heinrich G, Bye A, Najjar SM, et al. Both aerobic endurance and strength training programmes improve cardiovascular health in obese adults. Clin.Sci.(Lond) 2008 Nov;115(9):283-93.

29. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat.Rev.Immunol. 2006 Oct;6(10):772-83.

30. Jonk AM, Houben AJ, de Jongh RT, Serne EH, Schaper NC, Stehouwer CD. Microvascular dysfunction in obesity: a potential mechanism in the pathogenesis of obesity-associated insulin resistance and hypertension. Physiology.(Bethesda.) 2007 Aug;22:252-60.

31. Mazzone T. Adipose tissue and the vessel wall. Curr.Drug Targets. 2007 Nov;8(11):1190-5.

32. Cakir-Atabek H, Demir S, PinarbaSili RD, Gunduz N. Effects of different resistance training intensity on indices of oxidative stress. J.Strength.Cond.Res. 2010 Sep;24(9):2491-7.

33. Ouchi N, Walsh K. Adiponectin as an anti-inflammatory factor. Clin.Chim.Acta 2007 May 1;380(1-2):24-30.

34. Chen H, Montagnani M, Funahashi T, Shimomura I, Quon MJ. Adiponectin stimulates production of nitric oxide in vascular endothelial cells. J.Biol.Chem. 2003 Nov 7;278(45):45021-6.

35. Motoshima H, Wu X, Mahadev K, Goldstein BJ. Adiponectin suppresses proliferation and superoxide generation and enhances eNOS activity in endothelial cells treated with oxidized LDL. Biochem.Biophys.Res.Commun. 2004 Mar 5;315(2):264-71.

36. Guzik TJ, West NE, Pillai R, Taggart DP, Channon KM. Nitric oxide modulates superoxide release and peroxynitrite formation in human blood vessels. Hypertension 2002 Jun;39(6):1088-94.

37. Schwartz BG, Economides C, Mayeda GS, Burstein S, Kloner RA. The endothelial cell in health and disease: its function, dysfunction, measurement and therapy. Int.J.Impot.Res. 2010 Mar;22(2):77-90.

38. Sitia S, Tomasoni L, Atzeni F, Ambrosio G, Cordiano C, Catapano A, Tramontana S, Perticone F, Naccarato P, Camici P, et al. From endothelial dysfunction to atherosclerosis. Autoimmun.Rev. 2010 Oct;9(12):830-4.

39. Vanhoutte PM, Shimokawa H, Tang EH, Feletou M. Endothelial dysfunction and vascular disease. Acta Physiol (Oxf) 2009 Jun;196(2):193-222.

40. Forstermann U. Nitric oxide and oxidative stress in vascular disease. Pflugers Arch. 2010 May;459(6):923-39.

41. Landmesser U, Hornig B, Drexler H. Endothelial function: a critical determinant in atherosclerosis? Circulation 2004 Jun 1;109(21 Suppl 1):II27-II33.

42. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 1980 Nov 27;288(5789):373-6.

43. Ignarro LJ, Buga GM, Wood KS, Byrns RE, Chaudhuri G. Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. Proc.Natl.Acad.Sci.U.S.A 1987 Dec;84(24):9265-9.

44. Walther C, Gielen S, Hambrecht R. The effect of exercise training on endothelial function in cardiovascular disease in humans. Exerc.Sport Sci.Rev. 2004 Oct;32(4):129-34.

45. Moncada S, Higgs A. The L-arginine-nitric oxide pathway. N.Engl.J.Med. 1993 Dec 30;329(27):2002-12.

46. Ko SH, Cao W, Liu Z. Hypertension management and microvascular insulin resistance in diabetes. Curr.Hypertens.Rep. 2010 Aug;12(4):243-51.

47. Kingwell BA. Nitric oxide-mediated metabolic regulation during exercise: effects of training in health and cardiovascular disease. FASEB J. 2000 Sep;14(12):1685-96.

48. Vanhoutte PM. Endothelial dysfunction: the first step toward coronary arteriosclerosis. Circ.J. 2009 Apr;73(4):595-601.

49. Wolin MS, Davidson CA, Kaminski PM, Fayngersh RP, Mohazzab H. Oxidant--nitric oxide signalling mechanisms in vascular tissue. Biochemistry (Mosc.) 1998 Jul;63(7):810-6.

50. Yung LM, Leung FP, Yao X, Chen ZY, Huang Y. Reactive oxygen species in vascular wall. Cardiovasc.Hematol.Disord.Drug Targets. 2006 Mar;6(1):1-19.

51. Centers for Disease Control and Prevention, Overweight and Obesity Fact Sheet; 2010. http://www.cdc.gov/obesity/index.html. Assessed August 2, 2010.

52. National Institutes of Health, Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report; 1998. http://www.nhlbi.nih.gov/guidelines/obesity/ob_gdlns.pdf. Assessed August 16, 2010.

53. World Health Organization, Obesity and Overweight Fact Sheet; 2010. http://www.who.int/mediacentre/factsheets/fs311/en/index.html. Assessed August 16, 2010.

54. Magalang UJ, Rajappan R, Hunter MG, Kutala VK, Kuppusamy P, Wewers MD, Marsh CB, Parinandi NL. Adiponectin inhibits superoxide generation by human neutrophils. Antioxid.Redox.Signal. 2006 Nov;8(11-12):2179-86.

55. Zarkesh-Esfahani H, Pockley G, Metcalfe RA, Bidlingmaier M, Wu Z, Ajami A, Weetman AP, Strasburger CJ, Ross RJ. High-dose leptin activates human leukocytes via receptor expression on monocytes. J.Immunol. 2001 Oct 15;167(8):4593-9.

56. Lau DC, Dhillon B, Yan H, Szmitko PE, Verma S. Adipokines: molecular links between obesity and atheroslcerosis. Am.J.Physiol Heart Circ.Physiol 2005 May;288(5):H2031-H2041.

57. Napoleone E, Di SA, Amore C, Baccante G, di FC, Porreca E, de GG, Donati MB, Lorenzet R. Leptin induces tissue factor expression in human peripheral blood mononuclear cells: a possible link between obesity and cardiovascular risk? J.Thromb.Haemost. 2007 Jul;5(7):1462-8.

58. Fain JN. Release of interleukins and other inflammatory cytokines by human adipose tissue is enhanced in obesity and primarily due to the nonfat cells. Vitam.Horm. 2006;74:443-77.

59. Sowers JR. Endocrine functions of adipose tissue: focus on adiponectin. Clin.Cornerstone. 2008;9(1):32-8.

60. Apovian CM, Bigornia S, Mott M, Meyers MR, Ulloor J, Gagua M, McDonnell M, Hess D, Joseph L, Gokce N. Adipose macrophage infiltration is associated with insulin resistance and vascular endothelial dysfunction in obese subjects. Arterioscler.Thromb.Vasc.Biol. 2008 Sep;28(9):1654-9.

61. Meyers MR, Gokce N. Endothelial dysfunction in obesity: etiological role in atherosclerosis. Curr.Opin.Endocrinol.Diabetes Obes. 2007 Oct;14(5):365-9.

62. Li H, Forstermann U. Prevention of atherosclerosis by interference with the vascular nitric oxide system. Curr.Pharm.Des 2009;15(27):3133-45.

63. Sud N, Sharma S, Wiseman DA, Harmon C, Kumar S, Venema RC, Fineman JR, Black SM. Nitric oxide and superoxide generation from endothelial NOS: modulation by HSP90. Am.J.Physiol Lung Cell Mol.Physiol 2007 Dec;293(6):L1444-L1453.

64. Zou MH, Cohen R, Ullrich V. Peroxynitrite and vascular endothelial dysfunction in diabetes mellitus. Endothelium 2004 Mar;11(2):89-97.

65. Bahia L, Aguiar LG, Villela N, Bottino D, Godoy-Matos AF, Geloneze B, Tambascia M, Bouskela E. Relationship between adipokines, inflammation, and vascular reactivity in lean controls and obese subjects with metabolic syndrome. Clinics.(Sao Paulo) 2006 Oct;61(5):433-40.

66. Knudson JD, Payne GA, Borbouse L, Tune JD. Leptin and mechanisms of endothelial dysfunction and cardiovascular disease. Curr.Hypertens.Rep. 2008 Dec;10(6):434-9.

67. Fruhbeck G. The adipose tissue as a source of vasoactive factors. Curr.Med.Chem.Cardiovasc.Hematol.Agents 2004 Jul;2(3):197-208.

68. Vincent HK, Morgan JW, Vincent KR. Obesity exacerbates oxidative stress levels after acute exercise. Med.Sci.Sports Exerc. 2004 May;36(5):772-9.

69. Galili O, Versari D, Sattler KJ, Olson ML, Mannheim D, McConnell JP, Chade AR, Lerman LO, Lerman A. Early experimental obesity is associated with coronary endothelial dysfunction and oxidative stress. Am.J.Physiol Heart Circ.Physiol 2007 Feb;292(2):H904-H911.

70. Korda M, Kubant R, Patton S, Malinski T. Leptin-induced endothelial dysfunction in obesity. Am.J.Physiol Heart Circ.Physiol 2008 Oct;295(4):H1514-H1521.

71. Singh P, Hoffmann M, Wolk R, Shamsuzzaman AS, Somers VK. Leptin induces C-reactive protein expression in vascular endothelial cells. Arterioscler.Thromb.Vasc.Biol. 2007 Sep;27(9):e302-e307.

72. Chen C, Jiang J, Lu JM, Chai H, Wang X, Lin PH, Yao Q. Resistin decreases expression of endothelial nitric oxide synthase through oxidative stress in human coronary artery endothelial cells. Am.J.Physiol Heart Circ.Physiol 2010 Jul;299(1):H193-H201.

73. Verma S, Li SH, Wang CH, Fedak PW, Li RK, Weisel RD, Mickle DA. Resistin promotes endothelial cell activation: further evidence of adipokine-endothelial interaction. Circulation 2003 Aug 12;108(6):736-40.

74. Kougias P, Chai H, Lin PH, Lumsden AB, Yao Q, Chen C. Adipocyte-derived cytokine resistin causes endothelial dysfunction of porcine coronary arteries. J.Vasc.Surg. 2005 Apr;41(4):691-8.

75. Calabro P, Samudio I, Willerson JT, Yeh ET. Resistin promotes smooth muscle cell proliferation through activation of extracellular signal-regulated kinase 1/2 and phosphatidylinositol 3-kinase pathways. Circulation 2004 Nov 23;110(21):3335-40.

76. Burnett MS, Lee CW, Kinnaird TD, Stabile E, Durrani S, Dullum MK, Devaney JM, Fishman C, Stamou S, Canos D, et al. The potential role of resistin in atherogenesis. Atherosclerosis 2005 Oct;182(2):241-8.

77. Tedgui A, Mallat Z. Cytokines in atherosclerosis: pathogenic and regulatory pathways. Physiol Rev. 2006 Apr;86(2):515-81.

78. Virdis A, Santini F, Colucci R, Duranti E, Salvetti G, Rugani I, Segnani C, Anselmino M, Bernardini N, Blandizzi C, et al. Vascular generation of tumor necrosis factor-alpha reduces nitric oxide availability in small arteries from visceral fat of obese patients. J.Am.Coll.Cardiol. 2011 Jul 12;58(3):238-47.

79. Soskic SS, Dobutovic BD, Sudar EM, Obradovic MM, Nikolic DM, Djordjevic JD, Radak DJ, Mikhailidis DP, Isenovic ER. Regulation of Inducible Nitric Oxide Synthase (iNOS) and its Potential Role in Insulin Resistance, Diabetes and Heart Failure. Open.Cardiovasc.Med.J. 2011;5:153-63.

80. Muzaffar S, Jeremy JY, Angelini GD, Stuart-Smith K, Shukla N. Role of the endothelium and nitric oxide synthases in modulating superoxide formation induced by endotoxin and cytokines in porcine pulmonary arteries. Thorax 2003 Jul;58(7):598-604.

81. Leung FP, Yung LM, Laher I, Yao X, Chen ZY, Huang Y. Exercise, vascular wall and cardiovascular diseases: an update (Part 1). Sports Med. 2008;38(12):1009-24.

82. Caldefie-Chezet F, Poulin A, Vasson MP. Leptin regulates functional capacities of polymorphonuclear neutrophils. Free Radic.Res. 2003 Aug;37(8):809-14.

83. Nagaev I, Bokarewa M, Tarkowski A, Smith U. Human resistin is a systemic immune-derived proinflammatory cytokine targeting both leukocytes and adipocytes. PLoS.One. 2006;1:e31.

84. Silswal N, Singh AK, Aruna B, Mukhopadhyay S, Ghosh S, Ehtesham NZ. Human resistin stimulates the pro-inflammatory cytokines TNF-alpha and IL-12 in macrophages by NF-kappaB-dependent pathway. Biochem.Biophys.Res.Commun. 2005 Sep 9;334(4):1092-101.

85. Ouedraogo R, Gong Y, Berzins B, Wu X, Mahadev K, Hough K, Chan L, Goldstein BJ, Scalia R. Adiponectin deficiency increases leukocyte-endothelium interactions via upregulation of endothelial cell adhesion molecules in vivo. J.Clin.Invest 2007 Jun;117(6):1718-26.

86. Cao Y, Tao L, Yuan Y, Jiao X, Lau WB, Wang Y, Christopher T, Lopez B, Chan L, Goldstein B, et al. Endothelial dysfunction in adiponectin deficiency and its mechanisms involved. J.Mol.Cell Cardiol. 2009 Mar;46(3):413-9.

87. Shimabukuro M, Higa N, Asahi T, Oshiro Y, Takasu N, Tagawa T, Ueda S, Shimomura I, Funahashi T, Matsuzawa Y. Hypoadiponectinemia is closely linked to endothelial dysfunction in man. J.Clin.Endocrinol.Metab 2003 Jul;88(7):3236-40.

88. Ouchi N, Ohishi M, Kihara S, Funahashi T, Nakamura T, Nagaretani H, Kumada M, Ohashi K, Okamoto Y, Nishizawa H, et al. Association of hypoadiponectinemia with impaired vasoreactivity. Hypertension 2003 Sep;42(3):231-4.

89. Li MR, Deng G, Yu YR. [Effect of Adiponectin on endothelial dysfunction in obese rats]. Sichuan.Da.Xue.Xue.Bao.Yi.Xue.Ban. 2009 Jul;40(4):612-4, 627.

90. Shimabukuro M, Higa N, Asahi T, Oshiro Y, Takasu N, Tagawa T, Ueda S, Shimomura I, Funahashi T, Matsuzawa Y. Hypoadiponectinemia is closely linked to endothelial dysfunction in man. J.Clin.Endocrinol.Metab 2003 Jul;88(7):3236-40.

91. Dang PM, Elbim C, Marie JC, Chiandotto M, Gougerot-Pocidalo MA, El-Benna J. Anti-inflammatory effect of interleukin-10 on human neutrophil respiratory burst involves inhibition of GM-CSF-induced p47PHOX phosphorylation through a decrease in ERK1/2 activity. FASEB J. 2006 Jul;20(9):1504-6.

92. Dokka S, Shi X, Leonard S, Wang L, Castranova V, Rojanasakul Y. Interleukin-10-mediated inhibition of free radical generation in macrophages. Am.J.Physiol Lung Cell Mol.Physiol 2001 Jun;280(6):L1196-L1202.

93. Lee S, Park Y, Dellsperger KC, Zhang C. Exercise training improves endothelial function via adiponectin-dependent and independent pathways in type 2 diabetic mice. Am.J.Physiol Heart Circ.Physiol 2011 Aug;301(2):H306-H314.

94. Kaur K, Sharma AK, Dhingra S, Singal PK. Interplay of TNF-alpha and IL-10 in regulating oxidative stress in isolated adult cardiac myocytes. J.Mol.Cell Cardiol. 2006 Dec;41(6):1023-30.

95. Gunnett CA, Heistad DD, Berg DJ, Faraci FM. IL-10 deficiency increases superoxide and endothelial dysfunction during inflammation. Am.J.Physiol Heart Circ.Physiol 2000 Oct;279(4):H1555-H1562.

96. Manigrasso MR, Ferroni P, Santilli F, Taraborelli T, Guagnano MT, Michetti N, Davi G. Association between circulating adiponectin and interleukin-10 levels in android obesity: effects of weight loss. J.Clin.Endocrinol.Metab 2005 Oct;90(10):5876-9.

97. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, Bauman A. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Circulation 2007 Aug 28;116(9):1081-93.

98. Centers for Disease Control and Prevention. State Indicator Report on Physical Activity, 2010. Atlanta, GA: U.S. Department of Health and Human Services, 2010. Assessed August 20, 2010.

99. World Health Organization, Physical Inactivity: A Global Public Health Problem; 2010. http://www.who.int/dietphysicalactivity/factsheet_inactivity/en/index.html. Assessed August 10, 2010.

100. Varo JJ, Martinez-Gonzalez MA, De Irala-Estevez J, Kearney J, Gibney M, Martinez JA. Distribution and determinants of sedentary lifestyles in the European Union. Int.J.Epidemiol. 2003 Feb;32(1):138-46.

101. Stevens J, Cai J, Evenson KR, Thomas R. Fitness and fatness as predictors of mortality from all causes and from cardiovascular disease in men and women in the lipid research clinics study. Am.J.Epidemiol. 2002 Nov 1;156(9):832-41.

102. Wei M, Kampert JB, Barlow CE, Nichaman MZ, Gibbons LW, Paffenbarger RS, Jr., Blair SN. Relationship between low cardiorespiratory fitness and mortality in normal-weight, overweight, and obese men. JAMA 1999 Oct 27;282(16):1547-53.

103. Hu G, Lindstrom J, Valle TT, Eriksson JG, Jousilahti P, Silventoinen K, Qiao Q, Tuomilehto J. Physical activity, body mass index, and risk of type 2 diabetes in patients with normal or impaired glucose regulation. Arch.Intern.Med. 2004 Apr 26;164(8):892-6.

104. Hu G, Tuomilehto J, Silventoinen K, Barengo N, Jousilahti P. Joint effects of physical activity, body mass index, waist circumference and waist-to-hip ratio with the risk of cardiovascular disease among middle-aged Finnish men and women. Eur.Heart J. 2004 Dec;25(24):2212-9.

105. Dube JJ, Amati F, Stefanovic-Racic M, Toledo FG, Sauers SE, Goodpaster BH. Exercise-induced alterations in intramyocellular lipids and insulin resistance: the athlete's paradox revisited. Am.J.Physiol Endocrinol.Metab 2008 May;294(5):E882-E888.

106. Olson TP, Dengel DR, Leon AS, Schmitz KH. Moderate resistance training and vascular health in overweight women. Med.Sci.Sports Exerc. 2006 Sep;38(9):1558-64.

107. Laufs U, Wassmann S, Czech T, Munzel T, Eisenhauer M, Bohm M, Nickenig G. Physical inactivity increases oxidative stress, endothelial dysfunction, and atherosclerosis. Arterioscler.Thromb.Vasc.Biol. 2005 Apr;25(4):809-14.

108. Walsh JH, Bilsborough W, Maiorana A, Best M, O'Driscoll GJ, Taylor RR, Green DJ. Exercise training improves conduit vessel function in patients with coronary artery disease. J.Appl.Physiol 2003 Jul;95(1):20-5.

109. Harris MB, Slack KN, Prestosa DT, Hryvniak DJ. Resistance training improves femoral artery endothelial dysfunction in aged rats. Eur.J.Appl.Physiol 2010 Feb;108(3):533-40.

110. Parise G, Brose AN, Tarnopolsky MA. Resistance exercise training decreases oxidative damage to DNA and increases cytochrome oxidase activity in older adults. Exp.Gerontol. 2005 Mar;40(3):173-80.

111. Hornig B, Maier V, Drexler H. Physical training improves endothelial function in patients with chronic heart failure. Circulation 1996 Jan 15;93(2):210-4.

112. De FE, Cusi K, Ocampo G, Berria R, Buck S, Consoli A, Mandarino LJ. Exercise-induced improvement in vasodilatory function accompanies increased insulin sensitivity in obesity and type 2 diabetes mellitus. J.Clin.Endocrinol.Metab 2006 Dec;91(12):4903-10.

113. Moien-Afshari F, Ghosh S, Elmi S, Khazaei M, Rahman MM, Sallam N, Laher I. Exercise restores coronary vascular function independent of myogenic tone or hyperglycemic status in db/db mice. Am.J.Physiol Heart Circ.Physiol 2008 Oct;295(4):H1470-H1480.

114. Yasari S, Wang D, Prud'homme D, Jankowski M, Gutkowska J, Lavoie JM. Exercise training decreases plasma leptin levels and the expression of hepatic leptin receptor-a, -b, and, -e in rats. Mol.Cell Biochem. 2009 Apr;324(1-2):13-20.

115. Ishii T, Yamakita T, Yamagami K, Yamamoto T, Miyamoto M, Kawasaki K, Hosoi M, Yoshioka K, Sato T, Tanaka S, et al. Effect of exercise training on serum leptin levels in type 2 diabetic patients. Metabolism 2001 Oct;50(10):1136-40.

116. Kadoglou NP, Perrea D, Iliadis F, Angelopoulou N, Liapis C, Alevizos M. Exercise reduces resistin and inflammatory cytokines in patients with type 2 diabetes. Diabetes Care 2007 Mar;30(3):719-21.

117. Kriketos AD, Gan SK, Poynten AM, Furler SM, Chisholm DJ, Campbell LV. Exercise increases adiponectin levels and insulin sensitivity in humans. Diabetes Care 2004 Feb;27(2):629-30.

118. Christiansen T, Paulsen SK, Bruun JM, Ploug T, Pedersen SB, Richelsen B. Diet-induced weight loss and exercise alone and in combination enhance the expression of adiponectin receptors in adipose tissue and skeletal muscle, but only diet-induced weight loss enhanced circulating adiponectin. J.Clin.Endocrinol.Metab 2010 Feb;95(2):911-9.

119. Gokce N, Vita JA, Bader DS, Sherman DL, Hunter LM, Holbrook M, O'Malley C, Keaney JF, Jr., Balady GJ. Effect of exercise on upper and lower extremity endothelial function in patients with coronary artery disease. Am.J.Cardiol. 2002 Jul 15;90(2):124-7.

120. Kawano H, Fujimoto K, Higuchi M, Miyachi M. Effect of combined resistance and aerobic training on reactive hyperemia in men. J.Physiol Sci. 2009 Nov;59(6):457-64.

121. Quyyumi AA, Patel RS. Endothelial dysfunction and hypertension: cause or effect? Hypertension 2010 May;55(5):1092-4.

122. Martel GF, Hurlbut DE, Lott ME, Lemmer JT, Ivey FM, Roth SM, Rogers MA, Fleg JL, Hurley BF. Strength training normalizes resting blood pressure in 65- to 73-year-old men and women with high normal blood pressure. J.Am.Geriatr.Soc. 1999 Oct;47(10):1215-21.

123. Harris KA, Holly RG. Physiological response to circuit weight training in borderline hypertensive subjects. Med.Sci.Sports Exerc. 1987 Jun;19(3):246-52.

124. Varady KA, Bhutani S, Church EC, Phillips SA. Adipokine responses to acute resistance exercise in trained and untrained men. Med.Sci.Sports Exerc. 2010 Mar;42(3):456-62.

125. Joannides R, Haefeli WE, Linder L, Richard V, Bakkali EH, Thuillez C, Luscher TF. Nitric oxide is responsible for flow-dependent dilatation of human peripheral conduit arteries in vivo. Circulation 1995 Mar 1;91(5):1314-9.

126. Tagawa T, Imaizumi T, Endo T, Shiramoto M, Harasawa Y, Takeshita A. Role of nitric oxide in reactive hyperemia in human forearm vessels. Circulation 1994 Nov;90(5):2285-90.

127. Ohrvall M, Berglund L, Vessby B. Sagittal abdominal diameter compared with other anthropometric measurements in relation to cardiovascular risk. Int.J.Obes.Relat Metab Disord. 2000 Apr;24(4):497-501.

128. Tran ZV, Weltman A. Predicting body composition of men from girth measurements. Hum.Biol. 1988 Feb;60(1):167-75.

129. Tran ZV, Weltman A. Generalized equation for predicting body density of women from girth measurements. Med.Sci.Sports Exerc. 1989 Feb;21(1):101-4.

130. Miyazaki S, Hiasa Y, Takahashi T, Tobetto Y, Chen H, Mahara K, Ogura R, Miyajima H, Yuba K, Hosokawa S, et al. Waist circumference reduction is more strongly correlated with the improvement in endothelial function after acute coronary syndrome than body mass index reduction. J.Cardiol. 2010 Mar;55(2):266-73.

131. Fakhrawi DH, Beeson L, Libanati C, Feleke D, Kim H, Quansah A, Darnell A, Lammi-Keefe CJ, Cordero-MacIntyre Z. Comparison of body composition by bioelectrical impedance and dual-energy x-ray absorptiometry in overweight/obese postmenopausal women. J.Clin.Densitom. 2009 Apr;12(2):238-44.

132. Hendel HW, Gotfredsen A, Hojgaard L, Andersen T, Hilsted J. Change in fat-free mass assessed by bioelectrical impedance, total body potassium and dual energy X-ray absorptiometry during prolonged weight loss. Scand.J.Clin.Lab Invest 1996 Dec;56(8):671-9.

133. Hashimoto M, Akishita M, Eto M, Ishikawa M, Kozaki K, Toba K, Sagara Y, Taketani Y, Orimo H, Ouchi Y. Modulation of endothelium-dependent flow-mediated dilatation of the brachial artery by sex and menstrual cycle. Circulation 1995 Dec 15;92(12):3431-5.

134. Kizhakekuttu TJ, Gutterman DD, Phillips SA, Jurva JW, Arthur EI, Das E, Widlansky ME. Measuring FMD in the brachial artery: how important is QRS gating? J.Appl.Physiol 2010 Oct;109(4):959-65.

135. Phillips SA, Das E, Wang J, Pritchard K, Gutterman DD. Resistance and aerobic exercise protects against acute endothelial impairment induced by a single exposure to hypertension during exertion. J.Appl.Physiol 2011 Apr;110(4):1013-20.

136. Garatachea N, Cavalcanti E, Garcia-Lopez D, Gonzalez-Gallego J, de Paz JA. Estimation of energy expenditure in healthy adults from the YMCA submaximal cycle ergometer test. Eval.Health Prof. 2007 Jun;30(2):138-49.

137. American College of Sports Medicine. ACSM's Guidelines for Exercise Testing and Prescription. 7th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2006.

138. American College of Sports Medicine. American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. Med Sci Sports Exerc. 2009 Mar;41(3):687-708.

139. Hass CJ, Feigenbaum MS, Franklin BA. Prescription of resistance training for healthy populations. Sports Med. 2001;31(14):953-64.

140. Armstrong RB. Initial events in exercise-induced muscular injury. Med.Sci.Sports Exerc. 1990 Aug;22(4):429-35.

141. Quindry JC, Stone WL, King J, Broeder CE. The effects of acute exercise on neutrophils and plasma oxidative stress. Med.Sci.Sports Exerc. 2003 Jul;35(7):1139-45.

142. Jebb SA, Moore MS. Contribution of a sedentary lifestyle and inactivity to the etiology of overweight and obesity: current evidence and research issues. Med.Sci.Sports Exerc. 1999 Nov;31(11 Suppl):S534-S541.

143. Harris RA, Padilla J, Hanlon KP, Rink LD, Wallace JP. The flow-mediated dilation response to acute exercise in overweight active and inactive men. Obesity.(Silver.Spring) 2008 Mar;16(3):578-84.

144. McGowan CL, Levy AS, Millar PJ, Guzman JC, Morillo CA, McCartney N, MacDonald MJ. Acute vascular responses to isometric handgrip exercise and effects of training in persons medicated for hypertension. Am.J.Physiol Heart Circ.Physiol 2006 Oct;291(4):H1797-H1802.

145. Hambrecht R, Adams V, Erbs S, Linke A, Krankel N, Shu Y, Baither Y, Gielen S, Thiele H, Gummert JF, et al. Regular physical activity improves endothelial function in patients with coronary artery disease by increasing phosphorylation of endothelial nitric oxide synthase. Circulation 2003 Jul 1;107(25):3152-8.

146. Mestek ML, Westby CM, Van Guilder GP, Greiner JJ, Stauffer BL, DeSouza CA. Regular aerobic exercise, without weight loss, improves endothelium-dependent vasodilation in overweight and obese adults. Obesity.(Silver.Spring) 2010 Aug;18(8):1667-9.

147. Seligman BG, Polanczyk CA, Santos AS, Foppa M, Junges M, Bonzanini L, Nicolaidis G, Camey S, Lopes AL, Sehl P, et al. Intensive practical lifestyle intervention improves endothelial function in metabolic syndrome independent of weight loss: a randomized controlled trial. Metabolism 2011 Dec;60(12):1736-40.

148. Watts K, Beye P, Siafarikas A, Davis EA, Jones TW, O'Driscoll G, Green DJ. Exercise training normalizes vascular dysfunction and improves central adiposity in obese adolescents. J.Am.Coll.Cardiol. 2004 May 19;43(10):1823-7.

149. Alpert MA. Obesity cardiomyopathy: pathophysiology and evolution of the clinical syndrome. Am.J.Med.Sci. 2001 Apr;321(4):225-36.

150. Kasper EK, Hruban RH, Baughman KL. Cardiomyopathy of obesity: a clinicopathologic evaluation of 43 obese patients with heart failure. Am.J.Cardiol. 1992 Oct 1;70(9):921-4.

151. Duffy SJ, Castle SF, Harper RW, Meredith IT. Contribution of vasodilator prostanoids and nitric oxide to resting flow, metabolic vasodilation, and flow-mediated dilation in human coronary circulation. Circulation 1999 Nov 9;100(19):1951-7.

152. Green DJ. Exercise training as vascular medicine: direct impacts on the vasculature in humans. Exerc.Sport Sci.Rev. 2009 Oct;37(4):196-202.

153. Traub O, Berk BC. Laminar shear stress: mechanisms by which endothelial cells transduce an atheroprotective force. Arterioscler.Thromb.Vasc.Biol. 1998 May;18(5):677-85.

154. Grijalva J, Hicks S, Zhao X, Medikayala S, Kaminski PM, Wolin MS, Edwards JG. Exercise training enhanced myocardial endothelial nitric oxide synthase (eNOS) function in diabetic Goto-Kakizaki (GK) rats. Cardiovasc.Diabetol. 2008;7:34.

155. Lauer N, Suvorava T, Ruther U, Jacob R, Meyer W, Harrison DG, Kojda G. Critical involvement of hydrogen peroxide in exercise-induced up-regulation of endothelial NO synthase. Cardiovasc.Res. 2005 Jan 1;65(1):254-62.

156. Cannon JG, St Pierre BA. Cytokines in exertion-induced skeletal muscle injury. Mol.Cell Biochem. 1998 Feb;179(1-2):159-67.

157. Ispirlidis I, Fatouros IG, Jamurtas AZ, Nikolaidis MG, Michailidis I, Douroudos I, Margonis K, Chatzinikolaou A, Kalistratos E, Katrabasas I, et al. Time-course of changes in inflammatory and performance responses following a soccer game. Clin.J.Sport Med. 2008 Sep;18(5):423-31.

158. Faulkner JA, Brooks SV, Opiteck JA. Injury to skeletal muscle fibers during contractions: conditions of occurrence and prevention. Phys.Ther. 1993 Dec;73(12):911-21.

159. Peake JM. Exercise-induced alterations in neutrophil degranulation and respiratory burst activity: possible mechanisms of action. Exerc.Immunol.Rev. 2002;8:49-100.

160. Tidball JG. Inflammatory cell response to acute muscle injury. Med.Sci.Sports Exerc. 1995 Jul;27(7):1022-32.

161. Powers SK, Jackson MJ. Exercise-induced oxidative stress: cellular mechanisms and impact on muscle force production. Physiol Rev. 2008 Oct;88(4):1243-76.

162. Tidball JG. Interactions between muscle and the immune system during modified musculoskeletal loading. Clin.Orthop.Relat Res. 2002 Oct;(403 Suppl):S100-S109.

163. Fielding RA, Manfredi TJ, Ding W, Fiatarone MA, Evans WJ, Cannon JG. Acute phase response in exercise. III. Neutrophil and IL-1 beta accumulation in skeletal muscle. Am.J.Physiol 1993 Jul;265(1 Pt 2):R166-R172.

164. McKay BR, De LM, Johnston AP, O'Reilly CE, Phillips SM, Tarnopolsky MA, Parise G. Association of interleukin-6 signalling with the muscle stem cell response following muscle-lengthening contractions in humans. PLoS.One. 2009;4(6):e6027.

165. Balducci S, Zanuso S, Nicolucci A, Fernando F, Cavallo S, Cardelli P, Fallucca S, Alessi E, Letizia C, Jimenez A, et al. Anti-inflammatory effect of exercise training in subjects with type 2 diabetes and the metabolic syndrome is dependent on exercise modalities and independent of weight loss. Nutrition, Metabolism and Cardiovascular Diseases 2010 Oct;20(8):608-17.

166. Rolland C, Hession M, Broom I. Effect of weight loss on adipokine levels in obese patients. Diabetes Metab Syndr.Obes. 2011;4:315-23.

167. Varady KA, Tussing L, Bhutani S, Braunschweig CL. Degree of weight loss required to improve adipokine concentrations and decrease fat cell size in severely obese women. Metabolism 2009 Aug;58(8):1096-101.

168. Heffernan KS, Jae SY, Wilund KR, Woods JA, Fernhall B. Racial differences in central blood pressure and vascular function in young men. Am.J.Physiol Heart Circ.Physiol 2008 Dec;295(6):H2380-H2387.

169. Mulukutla SR, Venkitachalam L, Bambs C, Kip KE, Aiyer A, Marroquin OC, Reis SE. Black race is associated with digital artery endothelial dysfunction: results from the Heart SCORE study. Eur.Heart J. 2010 Nov;31(22):2808-15.

170. Schoeller DA. Limitations in the assessment of dietary energy intake by self-report. Metabolism 1995 Feb;44(2 Suppl 2):18-22.

171. Centers for Disease Control and Prevention. National Center for Health Statistics. Leading Causes of Death by Age Group, All Females, United States, 2006. Hyattsville, MD: Department of Health and Human Services; 2006.

172. Mosca L, Manson JE, Sutherland SE, Langer RD, Manolio T, Barrett-Connor E. Cardiovascular disease in women: a statement for healthcare professionals from the American Heart Association. Writing Group. Circulation 1997 Oct 7;96(7):2468-82.

173. Mittleman MA, Maclure M, Tofler GH, Sherwood JB, Goldberg RJ, Muller JE. Triggering of acute myocardial infarction by heavy physical exertion. Protection against triggering by regular exertion. Determinants of Myocardial Infarction Onset Study Investigators. N.Engl.J.Med. 1993 Dec 2;329(23):1677-83.

174. Bedinghaus J, Leshan L, Diehr S. Coronary artery disease prevention: what's different for women? Am.Fam.Physician 2001 Apr 1;63(7):1393-6.

175. Maas AH, van der Schouw YT, Regitz-Zagrosek V, Swahn E, Appelman YE, Pasterkamp G, Ten CH, Nilsson PM, Huisman MV, Stam HC, et al. Red alert for women's heart: the urgent need for more research and knowledge on cardiovascular disease in women: proceedings of the workshop held in Brussels on gender differences in cardiovascular disease, 29 September 2010. Eur.Heart J. 2011 Jun;32(11):1362-8.

VITA

NAME:	Nina Cherie Franklin
EDUCATION:	B.S., Kinesiology, University of Illinois at Urbana-Champaign, Urbana, Illinois, 2002
	Diploma, Clinical Massage Therapy, The Soma Institute, Chicago, Illinois, 2004
	M.S., Movement Sciences, University of Illinois at Chicago, Chicago, Illinois, 2006
	Ph.D., Kinesiology, Nutrition, and Rehabilitation, University of Illinois at Chicago, Chicago, Illinois, 2012
TEACHING:	Department of Kinesiology and Nutrition, University of Illinois at Chicago, Chicago, Illinois: Kinesiology and Nutrition: First-Year Seminar, 2010
	Department of Movement Sciences, University of Illinois at Chicago, Chicago, Illinois: Weight Training I, 2004-2006
	Department of Movement Sciences, University of Illinois at Chicago, Chicago, Illinois: Aerobic Conditioning I, 2004-2005
EXPERIENCE:	Complete Heath Solutions, L3C, Flossmoor, Illinois: Health and Wellness Consultant, 2005-Present
	Department of Physical Therapy, University of Illinois at Chicago, Chicago, Illinois: Graduate Research Assistant, 2008-Present
	Department of Kinesiology and Nutrition, University of Illinois at Chicago, Chicago, Illinois: Graduate Research Assistant, 2006-2008
	Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Northwestern Memorial Hospital, Chicago, Illinois: Massage Therapist, Intern, 2004
	Regents Club, Chicago, Illinois: General Manager, Group Exercise Instructor, Personal Fitness Trainer, and Health Fitness Consultant, 2003-2004

	Accelerated Rehabilitation Center, Chicago, Illinois: Physical Therapy Aide, 2002-2004
	Department of Campus Recreation, University of Illinois, Champaign, IL: Group Exercise Instructor, Personal Fitness Trainer, and Health Fitness Consultant, 1999-2002
HONORS AND AWARDS:	University of Illinois, Urban Health Program, Outstanding Student Achievement Award , 2012
	National Institutes of Health, Research Supplement Award, 2011
	Phi Kappa Phi, Honor Society for Academic Excellence, 2010
CERTIFICATIONS:	Group Exercise Instructor, Aerobic and Fitness Association of America, 2010
	Health Fitness Specialist, American College of Sports Medicine, 2010
	Massage Therapy, National Certification Board for Therapeutic Massage and Bodywork, 2005
	Personal Fitness Trainer, American Council on Exercise, 2001
PROFESSIONAL MEMBERSHIPS:	American Physiological Society, 2011
	American Heart Association, 2011
	American College of Sports Medicine, 2010
	Aerobics and Fitness Association of America, 2010
RESEARCH AWARDS:	Source: Massage Therapy Foundation Research Grant Project Title: Efficacy of Massage Therapy in Attenuating Vascular Dysfunction after Exertion-Induced Muscle Injury Dates: 09/01/2010-08/30/2011 Role: Principal Investigator Direct Funds: $30,000 (1 year)
ABSTRACTS:	Franklin, NC, Ali, M, Goslawski, M, Phillips, SA. Reduced Brachial Artery Smooth Muscle Function after Acute Exhaustive Resistance Exercise in Obesity. APTA, Cardiovascular and Pulmonary Platform Presentation, 2012.

Bian, JT, Yue, L, Franklin, NC, Mazzone, T, Phillips, SA. Exercise Training during Human Obesity Protects Against Impaired Microvascular Function after Acute Exertion by Enhancing Hydrogen Peroxide-Mediated Flow-Induced Dilation. AHA, Experimental Biology. 2012.

Franklin, NC, Ali, M, Goslawski, M, Phillips, SA. Impaired Vascular Function after Acute Exhaustive Resistance Exercise in Sedentary Lean and Obese Women. AHA, Heart, Lung, and Blood Institute. 2011.

Bian, JT, Goldufsky, J, Goslawski, M, Franklin, NC, Phillips, SA. Increased Endogenous Anti-oxidative Proteins and Endothelial Nitric Oxide Synthase Contribute to the Protective Effect of Chronic Exercise Against Microvascular Dysfunction Induced by Acute Exertion. AHA, Arteriosclerosis, Thrombosis and Vascular Biology. 2011.

Bian, JT, Franklin, NC, Yue, L, Goslawski, M, Ali, M, Walji, Z, Phillips, SA. Exercise Training Protects Against Impaired Microvascular Function after Acute Exertion by Enhancing the Mechanism of Flow-induced Dilation from NO to H2O2 in Human Obesity. AHA, Exercise, Physical Activity and Rehabilitation. 2011.

PUBLICATIONS:

Franklin, NC and Tate, CA. Successful Aging. In: Rippe, J, ed. Encyclopedia of Lifestyle Medicine and Health. Thousand Oaks, CA: Sage Publications, Inc, 2011.

Tate, CA and Franklin, NC. Reserve Capacity. In: Rippe, J, ed. Encyclopedia of Lifestyle Medicine and Health. Thousand Oaks, CA: Sage Publications, Inc, 2011.

Franklin, NC and Tate, CA. Lifestyle and Successful Aging: An Overview. Am J Lifestyle Med, 3: 6-11. 2009.