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Acute Effect of Resistance Exercise on Vascular and Cognitive Function

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Acute Effect of Resistance Exercise on Vascular and Cognitive Function

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Abstract

Introduction: The brain is impacted by increases in the stiffness of large extracranial vessels such as the aorta. Increased aortic stiffness has been shown to be associated with reduced cognitive function. While resistance exercise (RE) is known to be beneficial for overall health, one bout of RE acutely increases aortic stiffness. This study examined whether increased aortic stiffness from an acute bout of RE is associated with decreased cognitive function. **Methods:** Twenty participants (20±1 years; gender balanced) were studied on two separate occasions with one visit serving as the exercise condition and the other as a non-exercise control condition. Each visit consisted of two sets of cognitive testing separated by either an acute bout of RE or a non-exercise control condition (sitting, watching an emotionally neutral video). Cognitive function was assessed as reaction time and accuracy during memory, number matching and attention tasks. Aortic stiffness was measured via pulse wave velocity (PWV) using a brachial oscillometric device. **Results:** There was a condition-by-time interaction for PWV ($p<0.05$) driven by a significant 10.2% increase in PWV following RE ($p<0.05$) with no change in PWV following the non-exercise control ($p>0.05$). There were condition-by-time interactions for congruent and incongruent average reaction times for correct answers ($p<0.05$) driven by a significant decrease in reaction times following RE ($p<0.05$) with no change in reaction times following the non-exercise control ($p>0.05$). There were no other significant changes in cognitive performance. **Conclusion:** These results suggest that although acute RE increases aortic stiffness, shown by an increase in PWV, it does not detrimentally impact cognitive function, and even improved two measures of executive function. Additional studies are needed to investigate the chronic effects of RE training on arterial function and cognition.

Executive Summary

Cardiovascular disease is extremely prevalent in the United States due to a number of factors, with one report projecting that by the year 2030, 40% of U.S. adults will have at least one form of cardiovascular disease (69). These factors include lifestyle choices like smoking, high fat meals and physical inactivity in addition to genetic predisposition. Due to the widespread incidence of cardiovascular disease, further research is needed because clinicians have not been able to find suitable therapeutic approaches that reduce the number of people impacted and/or minimize the severity of the disease. Chronic high blood pressure (i.e. hypertension) is a prominent risk factor for cardiovascular disease. Although hypertension is a complex disease with multifaceted etiology, one notable cause of hypertension is arteriosclerosis or the stiffening of arteries. Stiff arteries and high blood pressure can have serious impacts on systemic health, especially in sensitive tissues like the eyes, lungs, kidneys and brain. Elastic arteries help buffer blood pressure pulsatility and protect target organs. Chronic high blood pressure combined with stiff arteries damages the brain due to forceful pulses of blood reaching the sensitive tissue. Stiff arteries also affect blood flow delivery to the brain and, therefore cognitive function, as less oxygen delivery has a detrimental effect on cognition. A therapeutic approach is needed in order to help slow the progression of chronic conditions like cardiovascular disease, high blood pressure and cognitive dysfunction.

Aerobic exercise has been extensively studied for its impact on blood pressure, vascular stiffness and cognitive function (4-6, 56). These studies have

shown the advantageous effects of aerobic training for overall health and specifically vascular function, manifesting as reductions in blood pressure and increases in arterial elasticity. The increase in vascular function has also been shown to have a favorable effect on cognitive function due to increased blood flow and oxygen delivery to the brain. Acute resistance exercise (e.g. weightlifting) is known to have a beneficial influence on overall health and in slowing the aging process, however the effect of resistance exercise on cognitive function, both in the short and long term, is not as well characterized. One bout of resistance exercise may have a negative effect on arterial function as select studies note that resistance exercise increases arterial stiffness, which theoretically would be detrimental for cognition (5). The present study examined whether increased artery stiffness stemming from acute resistance exercise had a negative effect on blood pressure pulses going to the brain and overall cognitive function.

Cognition is a process dependent on blood flow and proper oxygen delivery to the brain (5). Previous studies have shown that challenging mental activities place large demands on the brain and an increased supply of blood is needed to maintain proper function (22). Control of blood flow is a function of arterial stiffness, as the vessels soothe pressure pulses so that blood flows to target organs in a smooth fashion. Aerobic exercise has been shown to be beneficial to the elastic properties of the arteries, while following resistance exercise the elastic properties are diminished, and blood flow to the brain is decreased (17, 88). The increased demand for oxygen and lowered blood flow could lead to decreased cognitive function since the brain is not receiving the proper amount of oxygen (17, 60, 88).

In order to investigate the effect of acute resistance exercise training on arterial function, and how changes in blood pressure and arterial function affect cognitive performance, a scientific study with 20 participants was conducted, with gender equally balanced. Participants underwent an initial screening to evaluate their overall health. There were a total of three visits with the first serving as a screening visit and the second and third being the control and experimental conditions. During the first visit, participants were given a health history questionnaire and a cognitive screening test. Participants had their body composition measured, along with performing maximal bench press and biceps curl exercises. Finally, participants were familiarized with the cognitive tests used in the experimental trials in order to lessen the learning effect.

Prior to the second and third visits to the lab, participants were given a set of instructions to follow in preparation for the appointment. In the second visit, participants were randomly assigned to one of two conditions: resistance exercise or a non-exercise time control (sitting). Whichever condition was not performed during the second visit was conducted during the third visit. Resting blood pressure and cognitive function were measured, followed by either the experimental exercise or non-exercise time control condition. Following the completion of either exercise or the time control, blood pressure and cognitive function were measured again. The exercise condition in the study consisted of five sets of bench press and five sets of biceps curl. The non-exercise time control required participants to sit for 35 minutes and watch an emotionally neutral documentary on the Solar System.

Results of the study showed the expected increases in PWV and blood pressure, with no change in most of the cognitive testing, but slight improvements in the tests involving executive function were observed following resistance exercise. These results are consistent with previous literature on the effect of acute resistance exercise on arterial function and seem to suggest that an acute bout of RE may not negatively impact cognitive function as initially hypothesized, with some support for improvements in executive function.

This research question is important because it could help identify possible vascular and cognitive health implications of acute resistance exercise, and the results could lead to further research on this topic. The findings of this study could change the way that resistance exercise is perceived and could lead to new recommendations for exercise prescription for general health.

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Acknowledgments

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Introduction

High blood pressure and other cardiovascular diseases are at an epidemic level in this country and clinicians have not been able to find suitable therapeutic approach that reduce the number of people impacted and/or minimize the severity of the disease. These conditions occur due to poor lifestyle choices such as high fat meals and low physical activity levels. Chronic high blood pressure is a complex disease with many causes. One notable factor in the pathogenesis of hypertension is an inside-out process called arteriosclerosis whereby the vessel walls become less elastic and lose their ability to serve as mediators of pressure. Arterial stiffness and high blood pressure can have detrimental impacts on systemic health and recent studies support findings that artery stiffness has a profound impact on the brain (68, 69).

Chronic high blood pressure damages white matter of the brain due to the inability of stiff vessels to fully transform the flow of blood from pulsatile to laminar (smooth). Artery stiffness also increases blood pressure pulses to the brain, which affects blood flow delivery. Both structural brain changes and low oxygen availability have a detrimental effect on cognitive function (22). A suitable therapeutic approach is needed in order to help slow the progression of chronic conditions like cardiovascular disease, high blood pressure and cognitive dysfunction.

One novel concept gaining acceptance is the use of exercise in the treatment and prevention of such chronic conditions. There have been many studies on the effects of aerobic exercise on blood pressure, vascular stiffness and cognitive

function. These studies have validated the advantageous effects of both acute and chronic aerobic training for overall health as well as improved arterial function (70). This augmentation of arterial function manifesting as reduced stiffness has also been previously shown to have a favorable effect on cognitive function due to increased blood flow and oxygen delivery to the brain (22, 40, 65).

Resistance exercise is the use of weights to augment strength, anaerobic endurance and size of skeletal muscles. Acute resistance exercise is known to have a beneficial influence on overall health and in slowing the aging process, however the effect of resistance exercise (e.g. weightlifting) both in the short and long term on cognitive function is not yet clearly established (5). One bout of resistance exercise may have a negative effect on arterial function as select studies note that resistance exercise increases arterial stiffness (22, 65) and chronic resistance exercise training can worsen this stiffness (48).

This study will examine if increased artery stiffness stemming from acute resistance exercise has a negative effect on blood pressure pulses going to the brain and overall cognitive function (65).

Background

The ability to control blood flow is influenced by arterial stiffness. Elastic arteries stabilize pressure pulses so that blood flows to target organs in a laminar (smooth) fashion. Adequate cognitive function is contingent on blood flow to the brain and proper oxygen delivery, a process known as neurovascular coupling (5). Previous studies have shown that intense cognitive strain places increased demands on the brain and an augmented supply of blood is needed to maintain proper function (22). Aerobic exercise has been shown to be beneficial to the elastic properties of the arteries (56). However, following acute resistance exercise training, the elastic properties of arteries are diminished, possibly affecting blood flow delivery to the brain (17, 60, 88). The high demand for oxygen and lowered blood flow supply may negatively affect cognitive function since neurons are not able to function at their full potential.

The lack of research on this topic is surprising considering how many people lift weights as their primary method of physical activity, and although providing a definitive answer may not be possible, this study will attempt to move the conversation in the direction of investigating resistance exercise and its secondary effects in a more comprehensive manner. The theoretical model of the present study can be seen in Figure 1.

The goal of this study is to investigate the effect of acute resistance exercise against a non-exercise control condition in terms of changes in artery stiffness and cognitive function.

Aim 1

To determine whether an acute bout of resistance exercise negatively impacts measures of arterial stiffness, wave reflection magnitude and pulse pressure.

Hypothesis 1

An acute bout of resistance exercise will lead to increases in arterial stiffness, causing increases in wave reflection magnitude and higher pulse pressure.

Aim 2

To determine whether an acute bout of resistance exercise negatively impacts overall cognitive function, especially the domains of short-term memory, working memory, and executive function.

Hypothesis 2

Following an acute bout of resistance exercise, cognitive function will decline across all domains resulting in diminished performance on all assessments.

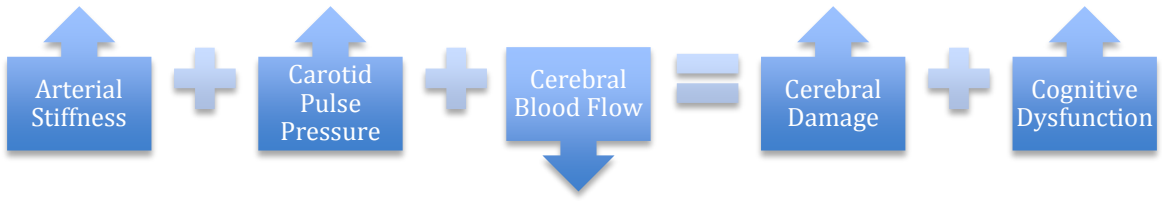

Figure 1: Theoretical Model of the Study.

Literature Review

High blood pressure and other cardiovascular diseases are at an epidemic level in this country and clinicians have not been able to find suitable therapeutic approaches that reduce the number of people impacted and/or minimize the severity of the disease. Significant evidence in the scientific literature now notes that increases in blood pressure may damage the brain and lead to cognitive decline. Both high blood pressure and cognitive decline occur due to poor lifestyle choices such as high fat diets and low physical activity levels. Chronic high blood pressure is a complex process due to many factors. One notable factor receiving considerable attention recently is an inside-out process called arteriosclerosis where the vessel walls become less elastic and lose their ability to serve as mediators of pressure. With a rapidly aging population, hypertension and its associated effects on the function of other biological systems will create an interesting dichotomy. Overall life expectancy has increased significantly in the past century, but along with advanced age comes a coincident decline in cognitive function, creating the question of whether advanced age without cognitive function is a suitable quality of life. Previous studies have shown that different modes of physical activity have diverse effects on blood pressure, the brain and cognitive function. The purpose of this literature review will be to explore the pertinent information on the cardiovascular system and its degeneration with age, the effect of vascular aging on cognitive function, the result of introducing different modalities of exercise on the vascular and cognitive systems, and to establish the theoretical rational for investigating the *Acute Effect of Resistance Exercise on Vascular and Cognitive Function*.

Cardiovascular

Vessel Anatomy and Aging:

Arteries contain three layers, the tunica intima which is made of thin endothelial cells in direct contact with the blood, the tunica media comprised of smooth muscle cells and elastin fibers, and the tunica adventitia which is mostly dense collagen fibers (7). A schematic representation of the artery can be seen in Figure 2. Throughout an organism's life cycle, there is constant regeneration and remodeling of the arteries. During the aging process and in response to stresses such as inflammation, the composition of the walls change with more remodeling taking place and fiber type changing (33). There is a gradual loss of flexible elastin fibers in the tunica media and an increase deposition of collagen fibers, which make the vessel less distensible and lead to an overall increase in thickness (15, 23, 76). More specifically, elastin synthesis is reduced while degradation increases, and Type 1 and 3 collagen fibers are deposited at an increased rate while their degradation is reduced (9). In addition, smooth muscle cells of the tunica adventitia undergo phenotypic changes to become stiffer and less reactive to contractile signaling (23). These coupled changes create an artery with less flexibility and a more rigid structure that is less responsive to change in pressure. In addition to changes in artery structure affecting vessel wall stiffness, there may also be changes in artery function. With aging, there is a decrease in endothelial function caused by a reduction in the bioavailability of nitric oxide (23, 67, 76). Nitric oxide is a powerful vasodilator, important in maintaining proper vascular tone and responding to fluctuations in blood pressure, but with aging, de-endothelialization concomitant

with inflammation/oxidative stress leads to diminished production of nitric oxide and larger fluctuations in blood pressure (67). All in all, these changes to the smooth muscle cells of the adventitia, elastic fibers of the media and endothelia of the intima create a vessel that is rigid and unable to perform in its usual capacity.

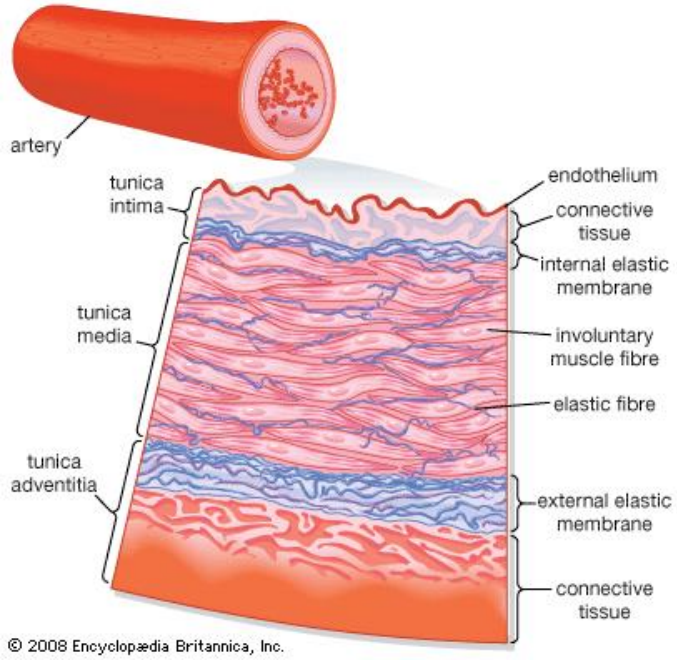

Figure 2: Overview of Vascular Anatomy.

Arterial Elasticity/Stiffness:

The ability to control blood pressure is multifactorial and partially dependent upon arterial elasticity. Elastic arteries stabilize pressure pulses so that blood flows to target organs in a laminar (smooth) fashion. A visual representation of these flow patterns can be seen in Figure 3. When blood is ejected from the heart, it has a pulsatile flow due to the rhythmic contraction of the heart. This pulsatile flow needs to be converted into a more usable and continuous flow so that organs of the body are receiving a consistent stream of oxygenated blood rather than rhythmic surges. The elasticity of the vessels varies along the arterial tree with the

aorta and other central vessels having the most elasticity as a result of their high elastin content, and the peripheral vessel having less elastic, and therefore less ability to modify blood pressure with the thoracic and abdominal aorta performing much of the buffering (9). Due to its high elastin content, the aorta acts a reservoir, buffering the pulsatile energy, decreasing the afterload, and preventing the delivery of detrimental high-energy blood to the end organs (7, 16). An example of this buffering capability can be seen in Figure 4.

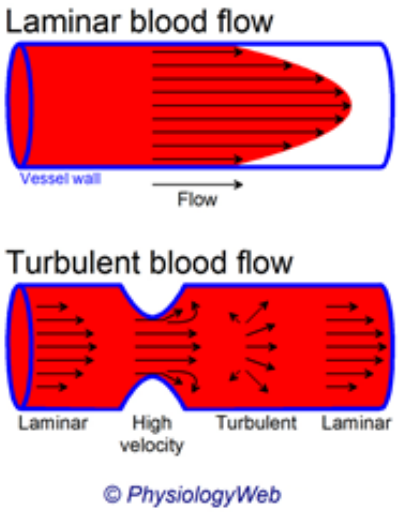

Figure 3: Examples of Laminar and Turbulent Blood Flow.

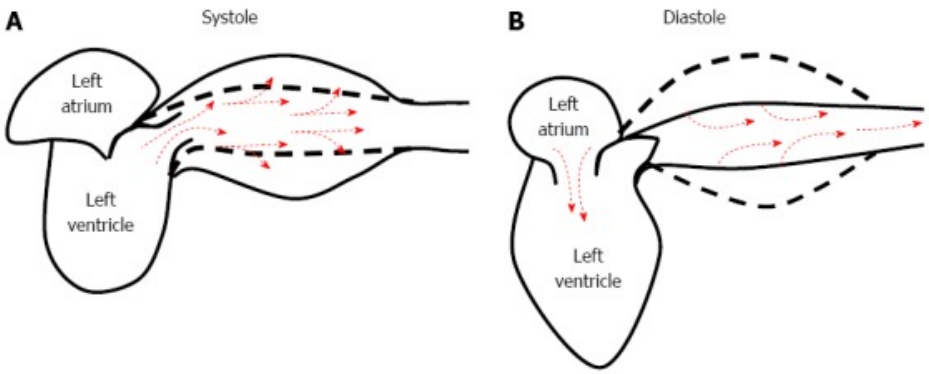

Figure 4: Role of Arterial Compliance in the Damping of Blood Flow and the Pressure Oscillations Generated by the Heart. Reproduced from (89).

Changes to vascular wall anatomy and physiology occur dynamically throughout the lifetime, with endothelial cells being replaced every few years and vascular smooth muscle cell modulation occurring at a faster rate (23). As we age, modifications in vascular anatomy occur, leading to structural and physiological variations in how our vessels function (9). The walls of large conduit arteries, such as the aorta, thicken and lose elasticity over time, becoming stiffer and reducing the reservoir function and lessening their buffering capability (9, 16, 76). The complex structure of large compliance vessels is preserved by virtue of a well-regulated equilibrium between its two extracellular matrix proteins, collagen and elastin (15). This transformation of vessel structure is as a result of gradual fragmentation and loss of elastin fibers and accumulation of stiffer collagen fibers in the tunica media (15, 34, 76). This degradation of elastin fibers may be caused by upregulation of matrix metalloproteinases, as previous studies have shown that their inhibition preserves elastin fibers, and eradicates collagen deposition (33, 76). Vascular smooth muscle cells, which were once pliable and responsive to hemodynamic change, undergo a phenotypic change becoming stiff and unresponsive (23). In a review by Mitchell, it was concluded that in the relationship between arterial stiffness and hypertension, the degradation of elastin in the vessel walls and the formation of rigid collagen fibers are associated with later development of hypertension (46).

A second simultaneous mechanism of arterial properties changing and overall distensibility decreasing is endothelium dysfunction, with stiffness increasing as dysfunction increases (67). With age, there is a gradual loss of

endothelial tissue, which plays an important role in the maintenance of normal vascular properties (23, 67). Nitric oxide is released by endothelial cells causing smooth muscle relaxation and vasodilation. Loss of endothelium with aging blunts the ability of the vessels to effectively regulate diameter and quickly respond to changes in blood pressure (9, 67). Nitric oxide not only causes vasodilation but also prevents other detrimental mechanisms of vascular damage such as platelet aggregation, vascular smooth muscle cell proliferation and monocyte adhesion, demonstrating the great importance of this signaling molecule (9).

The structural remodeling of the vessel wall along with the functional loss of vasodilatory nitric oxide create a stiffer vessel less able to respond to stress and fluctuations in blood pressure. This stiffening of the vessel wall, loss of elasticity and inability to quickly vasodilate characterize an artery with decreasing compliance (23). This loss of compliance leads to greater swings in blood pressure (BP), pulse pressure augmentation and impaired cardiac function (16). Greater aortic stiffness has been associated with incident hypertension and greater blood pressure increases over time caused by increased stroke work of the left ventricle, leading to left ventricular hypertrophy (7, 16).

Pulse Wave Velocity:

Following the changes in vascular structure and function, there are accompanying changes in blood pressure manifesting as increased velocity of blood pressure waves throughout the body. This change could be quantified as an alteration of pulse wave velocity (PWV), defined as the velocity at which the

pressure waves generated by the systolic contraction of the heart propagate along the arterial tree (55, 89). The measurement and evaluation of PWV gives essential information about the elastic properties of the vessels, with a higher PWV being analogous to higher arterial stiffness (55). Throughout our lifetime, aortic wall stiffness (as measured by PWV) varies, with steady increases throughout ending with an immense transformation (46). In normally functioning vessels, blood flows at a relatively consistent velocity with modifications being mediated by the stiffness of the vessel wall and the release of nitric oxide. Pulse wave velocity is defined by mean arterial pressure and intrinsic stress/strain relationship (stiffness) of the arterial wall (23). With a decrease in the ability of large vessels to buffer disordered blood flow, the velocity of the blood pressure waves increases as they reach the aortic bifurcation (89). This scenario leads to the formation of a reflected wave, following the normal physiological pattern, with the main difference being the speed of the reflected wave and where it overlaps the forward wave (89). The forward or incident pressure wave originates in the left ventricle and is propagated within the aorta to arteries throughout the body (89). As the forward wave travels along, progressive changes in the tunica media cause arterial stiffness to grow from the aorta to distal muscular arteries, with complementary increases in PWV (55, 89). The increasing stiffness of the vessel walls, along with alterations in aortic geometry, arterial branching and luminal narrowing, cause partial reflections of the forward pressure waves (89). The reflected pressure waves travel back to the central aorta, where they affect the amplitude of the systolic blood pressure and pulse pressure throughout the aortic tree (89). As elastic and muscular arteries

become stiffer due to age or break down due to inflammation and disease, both the forward and backward pressure pulse waves proliferate faster leading to a premature return of the reflected wave to the ascending aorta and a shift in the appearance of the pulse wave (89). In younger subjects and healthy individuals, the buffering capability of the arteries controls the forward pulse wave and the reflected wave intersects with the next forward wave during the diastolic phase of the cardiac cycle (89). Patients with stiffer arteries, as typically seen with advanced age and in those suffering from disease, will have a faster pulse wave velocity as much of the buffering capability is lost, leading to a faster reflection of the forward wave and an intersection with the next forward wave during systole (89). The overlap of the first reflected wave with the second forward wave during systole raises systolic blood pressure as the two waves combine, while also lowering diastolic pressure due to the fact that where overlap customarily occurs, there will only be a forward wave, as seen in Figure 5 (89).

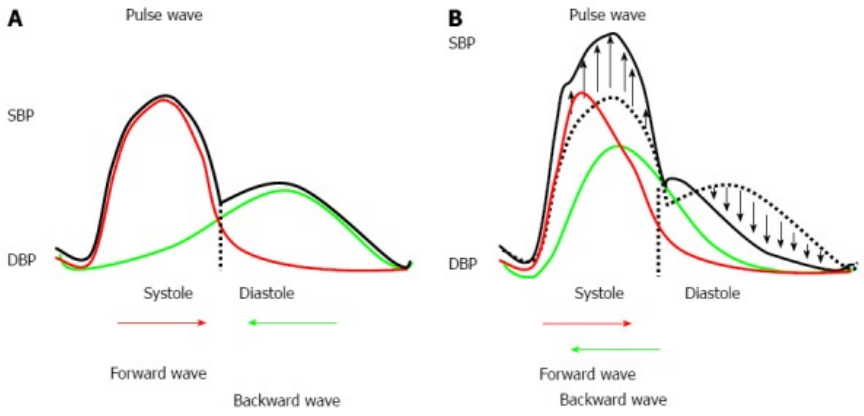

Figure 5: Arterial Stiffness and Reflection Waves. Reproduced from (89).

Central Hemodynamics:

Although peripheral measures of blood pressure are commonly measured and easily accessible, they are not the most informative measures when attempting to evaluate cardiovascular health and discover risk of disease. A more informative location to take these measures would be just outside the aorta as it is the conduit between the heart and peripheral vascular system and plays an important role in the delivery of blood to smaller arteries and eventually target end organs (62, 77, 86). Blood pressure has two distinct phases, the systolic wave is larger and occurs while the heart is contracting, pushing blood out to the body and the diastolic phase, which occurs during diastole or the relaxation of the myocardium, as seen in Figure 6. Mean arterial pressure provides an estimation of the average pressure felt by the vessel during one cardiac cycle and is calculated as two times diastolic pressure plus systolic pressure divided by three (16). Pulse pressure is defined as the difference between systolic and diastolic values and gives an indication of the force generated by the heart with each beat (16, 46). Elevated mean and diastolic pressures are indicative of high systemic vascular resistance and severe atherosclerosis, both of which characterize malignant hypertension (32). In comparison with systolic pressure however, diastolic pressure is not as clinically relevant. Systolic pressure increases throughout the lifetime while diastolic increases until middle age and then declines (32). This continued increase in systolic pressure along with the accompanying rise in pulse pressure is more closely related with cardiovascular disease risk, as verified by the Framingham studies (16, 32, 46). During the first half of systole, blood pressure is determined by the interaction between the forward

moving wave and the stiffness of the aorta (as described above), while in the second half of systole the diminishing forward wave is augmented by the reflected wave produced at the aortic bifurcation (32). The size of the reflected wave is described by augmentation index, the ratio of the height of the second systolic pressure wave peak to first systolic pressure wave peak (16, 32, 77). Augmentation index is affected by systemic vascular resistance and pulse wave velocity, with a higher pulse wave velocity leading to an earlier return of the reflected wave and a greater overlap of the waves (32). Diastolic blood pressure is relatively constant in an individual, while systolic pressure and pulse pressure vary greatly in an individual (32). Pulse pressure is sensitive to the stiffness of the aortic wall in addition to the magnitude of the reflected wave and the ventricular interaction with a given reflected wave (46). This increase in pulse pressure increases pulsatile aortic wall stress, accelerating the degradation of elastin fibers (46). Pulse pressure amplification is a property of both arteries producing pulse pressure and systolic pressure amplification due to narrowing of the arterial diameter and greater impendence to flow (32). This value varies greatly throughout the body, with the brain and kidneys having extensive branching patterns causing very little pulse pressure amplification and putting them at risk for "barotrauma" caused by the transfer of increased pulse pressure to the tissue (32). Systolic pressure and pulse pressure are affected to a greater extent by physiological and environmental stressors in comparison with diastolic pressure, thus making them good targets for cardiovascular disease risk assessment (32).

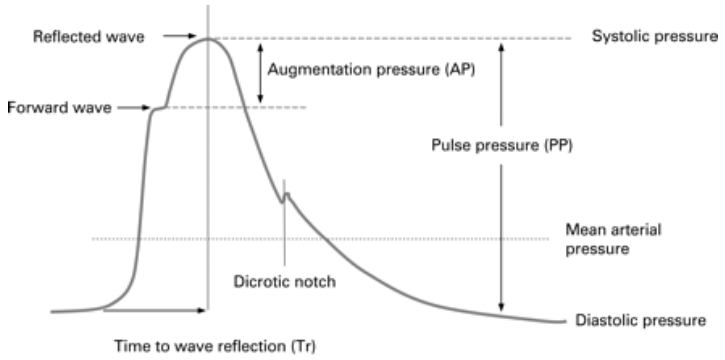

Figure 6: An Aortic Pulse Waveform as Produced by the SphygmoCor System from Applanation Tonometry of the Radial Artery. Reproduced from (45).

As we age, central hemodynamic values vary with alterations in vascular anatomy and function, creating age related hypertension. Systolic pressure and arterial stiffness increase with age, while systemic resistance and augmentation index increase until age 60 then level off; diastolic pressure declines and pulse pressure increases after age 60 (32). This increase in systolic pressure is associated disproportionately with central pressure changes rather than brachial pressure, lowering aortic to radial pulse pressure (32). With the stiffening of central vasculature, variations in wave reflections occur and cause dramatic changes in blood pressure waves, as seen in Figure 7. Due to the short distance from the aortic valve to its bifurcation in the lower trunk and the high speed of the forward wave, the variation in the timing of the reflected wave is less than 50 milliseconds, but it has severe implications (32). Wave reflections are useful in aiding the closure of the aortic valve and maintaining upward blood flow to the brain; however, with an excessive wave reflection, there is an increased systolic load and myocardial hypertrophy of the left ventricle (32). A summary of all hemodynamic terminology can be seen in Table 1.

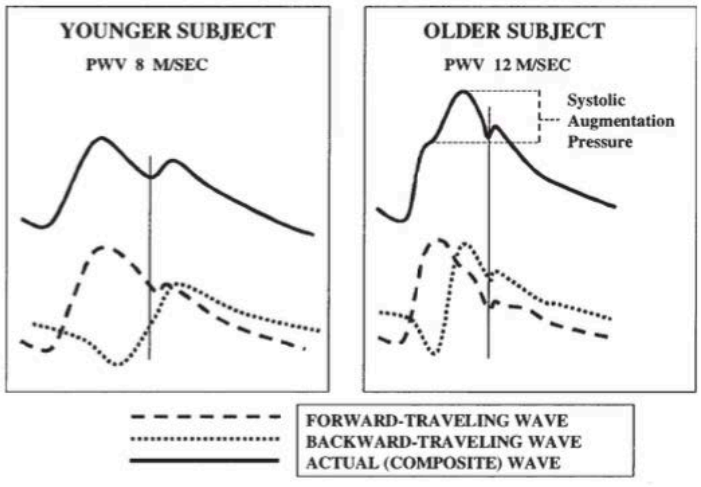

Figure 7: Components of Arterial Pulse Waves in Older and Younger Subjects. Reproduced from (31).

Table 1: Summary of Hemodynamic Terminology.

Arterial Compliance	The ratio of a volume change caused by a given pressure change in a hollow distensible tube
Arterial Stiffness	Used to signify the inverse of compliance
Distensibility	The relationship between the fractional change in compliance and the corresponding change in cross-sectional area or volume
Elastance	The tendency of a hollow organ to recoil to its original dimension with decreases in blood pressure
Pulse Wave Velocity (PWV)	The speed at which a blood pressure wave moves throughout the body
Augmentation Index (AIx)	Measure of increases in central aortic systolic blood pressure caused by a reflected pulse wave

Clinical Measures:

In order to measure arterial stiffness and wave reflections, pulse wave velocity, a noninvasive applanation tonometer is utilized. This method is considered the gold standard, as it is simple to perform, easily reproducible and has immense clinical use in the predication of aortic stiffness and future cardiac events (9). Pulse wave velocity can be measured across a number of different sites, but the most

common location is transcutaneous at the common carotid and femoral arteries, as seen in Figure 8 (9). The length between the two measurement sites is recorded and the time from the foot of one wave to the foot of the next is recorded. The distance between the two sites is often calculated by measuring distance from the suprasternal notch to femoral artery, and suprasternal notch to carotid artery (4, 14, 26). The distance from the suprasternal notch to carotid artery is then subtracted from the other measure in order to take into account variance in direction of pulse wave propagation estimated using the foot-to-foot method, with the foot of a wave being defined as the end of diastole, just before the onset of next forward moving wave (4, 9, 14, 26). Pulse wave velocity is calculated as the relationship between the distance traveled and the time over which the wave propagated, as seen in Figure 9 (9). These waves are recorded sequentially at the carotid and femoral arteries and a synchronized electrocardiogram (EKG) is used as a time marker (4, 9, 14, 26).

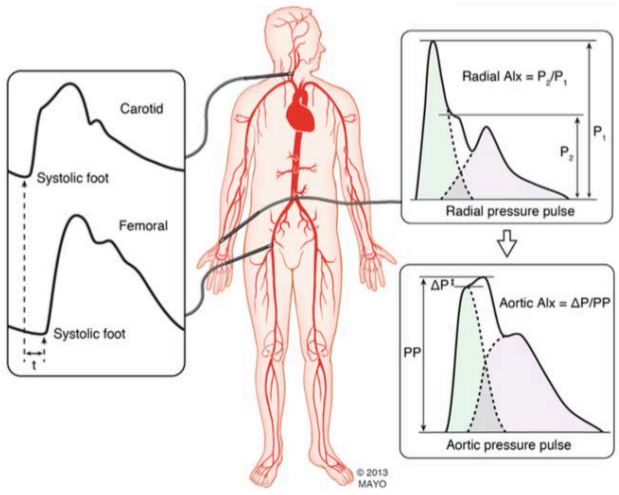

Figure 8: Carotid-Femoral Pulse Wave Velocity (cfPWV) and Central Arterial Waveform Assessment Using Arterial Applanation Tonometry. Reproduced from (15).

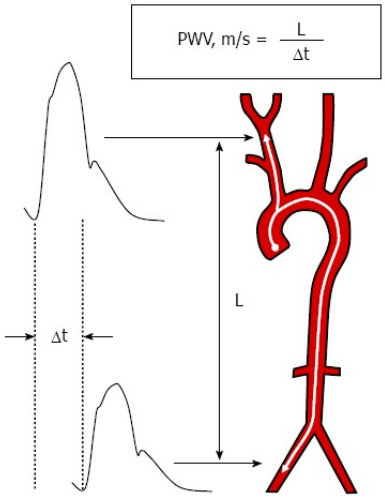

Figure 9: Reference Technique Utilized to Measure Carotid-Femoral Pulse Wave Velocity. Reproduced from (89).

While estimation of pulse wave velocity using applanation tonometry is considered the best method ("gold standard") and yields excellent results for a noninvasive technique, the time intensive nature and training associated with this method make it not suitable for all situations. Therefore, there was a need for a less complex device giving the same values, while allowing the researcher or practitioner to gather other data. The Mobil-O-Graph is the solution to this problem. It can be placed on the brachial artery similar to a traditional blood pressure cuff, but it gives measures comparable to more time consuming techniques (62, 86). The Mobil-O-Graph is an automated oscillometric device giving values of central blood pressure, using a mathematical equation called a generalized transfer function (32, 86). This formula allows brachial pulse waves from an oscillometric blood pressure cuff to be transformed into estimations of central aortic pressure (86). In a recent study, the Mobil-O-Graph with ARCSolver equation was validated against an invasive measure of central aortic stiffness using pressure sensing catheters placed 1cm above the aortic valve, with simultaneous measures being recorded in the left

arm using the Mobil-O-Graph (86). Overall, the study found that the measurements recorded by the Mobil-O-Graph were valid in comparison to highly invasive matched measures, and that while there are some limitations of the device, it performed remarkably well for a noninvasive method and allowed comparison of central and peripheral blood pressure (32, 86).

Effect of Arterial Stiffness on Systemic Health:

Artery stiffness and high blood pressure can have serious detrimental impacts on systemic health and recent studies support that artery stiffness has a profound impact on the heart, brain, and kidneys along with increasing risk of mortality (15, 16, 23, 34, 76). The lack of buffering by the aorta and other large arteries cause an incomplete transition of blood flow from turbulent to laminar, meaning that there is still some pulsatile energy left, which is then transferred to the target organs, as seen in Figure 10 (15, 33, 75). Studies have shown that this detrimental flow impairs the function of many of the most important systems in the body (16). Chronic hypertension and increased cardiac work ultimately contribute to cerebrovascular accidents and/or myocardial infarction (23, 70, 76). More specifically, reduced large artery compliance leads to left ventricular hypertrophy, a prolonged myocardial contraction, and reduced early diastolic filling amounting to a weakened heart unable to properly circulate blood (33, 70). In addition, the stiffening of the ascending aorta and carotid sinus cause less deformation of the arterial wall, and therefore less afferent signaling by the arterial baroreceptors leading to a smaller efferent response (70). Diminished signaling by the cardiovagal

innervation leads to increased pressure variability, decreased ability to resist ventricular fibrillation, especially with myocardial ischemia, and elevated risk of sudden cardiac death (70).

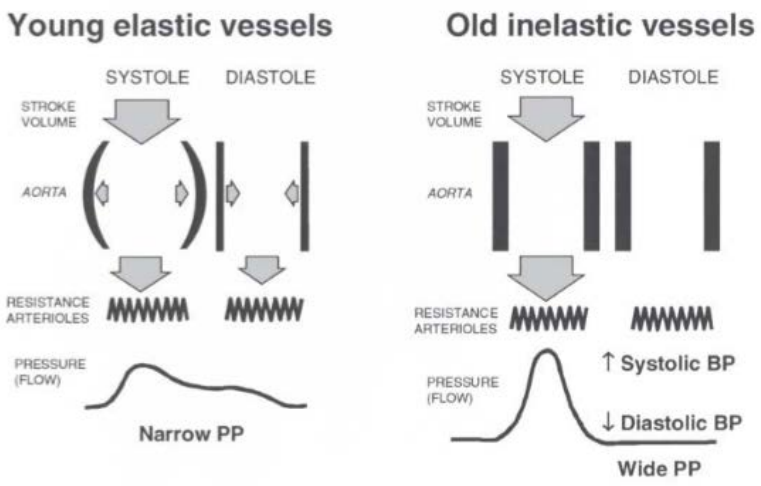

Figure 10: Effect of Central Arterial Stiffness on Pulse Pressure. Reproduced from (31).

In addition to harming the cardiovascular system, pulsatile flow creates havoc in the kidneys, a very fragile tissue and the site of blood filtration for waste removal (9, 33, 76). Previous studies have found that in patients with chronic kidney disease subclinical damage to the large arteries is frequently observed, predominantly characterized by an augmented stiffness of the large arteries coupled with maladaptive arterial remodeling (34). These findings reinforce the well-known adage that arterial stiffness, measured by carotid-femoral pulse wave velocity, has a strong predictive effect on overall mortality in the general population along with patients suffering from end stage renal disease, hypertension and coronary heart disease (34). Overall, this relationship can be correlated to compromised coupling between the heart and vessels, excessive wave reflections due to arterial stiffening,

and the eventual transmission of these wave reflections to the periphery causing end organ damage (34).

Along with the damage done to the heart and kidneys, increases in arterial stiffness and associated hemodynamic fluctuations can cause detrimental effects on the brain and cognitive system (9, 33). These changes to the cognitive system can be extremely harmful and lead to diseases like Alzheimer's and dementia.

Cognitive

Anatomy of Cognition:

The brain is a complex organ with interactions between physical structures and cognitive pathways. The prefrontal cortex plays an important role in cognition, allowing us to switch between tasks (35). Tasks involving complex problem solving and planning are integrated in the anterior part of the frontal lobes, particularly the fronto-polar prefrontal cortex (FPPC) (35). This portion of the frontal lobe allows for dual task performance by allocating attentional resources in order to focus on a pressing task, a process called branching (35). This process is necessary in everyday life and allows for processing of concurrent tasks by allowing for the more imperative task to be completed first while relevant information for the other task is stored in working memory so that it can be subsequently completed (35). Another particularly interesting area of cognitive functioning still being explored is the concept of the default network. This area is important in understanding cognition because it is active when individuals are left to think on their own, in the absence of external task direction (10). The default network challenges the popular belief that

when the brain is left undirected, it is idle. In fact, quite the opposite is true with increased activity during rest being localized to the prefrontal cortex, where other important domains of cognition reside (10).

Since the brain cannot store energy within its tissues, proper function depends on continuous delivery of oxygen and glucose through blood flow (57). In order to assure that there is always adequate perfusion of the brain, there is a close spatial and temporal relationship between neurologic activity and cerebral blood flow, called neurovascular coupling (20). Under normal physiological conditions, neurovascular coupling occurs between activation of specific brain function and microcirculation flow activation, with microvessels, endothelial cells, neurons, and glial cells closely integrated (20, 57, 74). Regulation of cerebral blood flow is not static, with localized regions having the ability to alter flow based on miniscule fluctuations in oxygen demand of the surrounding tissue (74). The exact mechanisms by which neurovascular coupling acts are very complex, and therefore will not be discussed in this review but include vasoactive ions, metabolic byproducts, vasoactive neurotransmitters, and vasoactive factors released in response to neurotransmitters (20).

The brain is a high-flow organ with a high metabolic rate, receiving 15% of the total cardiac output, even though it only accounts for 2% of the total body weight (57). Large cerebral arteries begin at the Circle of Willis and branch out into smaller arteries and arterioles ending with cerebral capillaries, which have a high density and a low smooth muscle content (20). Brain endothelial cells are distinctive in that they are not fenestrated and are sealed by tight junctions, forming the blood-

brain barrier (20). Blood flow to the brain is normally autoregulated, implying that flow remains constant over a wide range of perfusion pressures (20, 29, 57). With stiffening of the vessels caused by aging or progression of cardiovascular disease, PWV increases and flow to the brain becomes more pulsatile, limiting blood flow, leading to cerebral hypoperfusion and a theoretical cascade to cognitive decline (57, 80). In Alzheimer's disease, neurovascular coupling is severely disrupted with cerebral microvessels being reduced in number, the flattening of endothelial cells and smooth muscle degeneration (20). These structural modifications come with accompany changes in function as resting cerebral blood flow is reduced and the surge in cerebral blood flow caused by activation is attenuated (20).

Effect of Aging on Cognition:

As we age, fluid intelligence decreases along with a decline in cognitive function (54, 57). Although loss of function occurs across all systems in the body, damage to the cognitive system is especially harmful since it has profound social and physiological conditions, which results in a loss of independence (74). Cognitive reserve is a functional concept related to the brain's ability to cope with increasing activity or damage (57). It states that brain plasticity allows increasing brain connectivity after strenuous mental activity throughout the lifetime and prolongs maintenance of function despite cell deterioration in old age (57). With decreases in cognitive function across the lifespan, a threshold is eventually reached where cognitive reserve can no longer account for losses in function and impairment becomes evident (57). Dementia is a debilitating condition of the brain occurring

predominantly in older adults, characterized by impairments in memory and other cognitive functions and ultimately disability and mortality (63, 73, 90). While normal aging causes brain atrophy of 4% for every ten years above age 65, neurodegenerative diseases such as vascular dementia and Alzheimer's disease accelerate the progression (57, 74). These deficiencies are severe enough to interfere with regular activities and occur in multiple cognitive domains, as the definition of dementia states that it must occur in two domains for it to be clinically relevant (63, 90). With an aging population both in the United States and around the world, understanding the mechanisms by which this disease acts and the developmental risk factors may lead to the implementation of preventative measures that can be taken to slow the progression and push back the onset of symptoms (73, 90). Alzheimer's disease is the most clinically common form of dementia, accounting for 75% of all cases, and is characterized by the deposition of amyloid β-peptide plaques in the brain (20, 63). Recent studies have found that changes in vascular physiology lead to cognitive decline and in fact account for a majority of dementia cases, challenging the notion that vascular dementia and Alzheimer's disease are separate entities (57, 63, 90). This idea that both vascular dementia and Alzheimer's disease can coexist, manifesting together as cognitive decline, has increased interest in examining the prevalence of dementias caused by amyloid plaques and vascular pathology (57). While there are many causes of dementia and other forms of cognitive decline, this literature review will mainly focus on the contribution of the cardiovascular system in cognitive decline (63, 73). Findings from these studies propose that dementia and cardiovascular diseases

share common risk factors such as hypertension, dyslipidemia, diabetes mellitus and smoking (57, 63, 73). While cognition naturally deteriorates with age, exposure to these common vascular risk factors (VRFs) create an acceleration of functional decline (63). The cause for concern with this progression is that younger individuals with exposure to one or multiple VRFs may suffer from mild cognitive impairment at a younger age than previously seen, with more severe impairment not far behind (63).

In the past twenty years, there has been increasing evidence of a link between the presence of VRFs and cognitive impairment or dementia (63). Community-based studies such as the Framingham Study, the Rotterdam Study and the Cardiovascular Health Study have all found an association between individual VRFs and cognitive decline or dementia, with particularly interesting effects between cardiometabolic risk factors, such as hypertension or hyperlipidemia and age, on the likelihood of developing cognitive impairment (63). The presence of VRFs with or without subsequent treatment in middle age (40-59 years of age) is associated with later cognitive decline, while after age 75 the association is less definite (63).

While there are many components in the association between cardiovascular disease and cognitive decline such as coronary heart disease, atrial fibrillation, heart failure, peripheral artery disease and carotid atherosclerosis, the most relevant factor for this literature review pertains to the age-associated changes in arterial stiffness (63). As previously mentioned, arterial stiffness measured using PWV can be a marker for subclinical cardiovascular disease, with cross sectional studies

reporting an association between increased stiffness and decreased cognitive function (54, 63, 73, 90). While arterial stiffness can be used as a determinant of cardiovascular health, it is still only a predictor of cognitive performance, decline and dementia (54). In a majority of cross sectional studies, it was concluded that greater arterial stiffness is associated with inferior cognitive function, with most recording the change in global cognitive performance, while among those studying individual cognitive domains, there was not a consistent association across the studies (73, 83, 90). A consensus has not been reached on this effect in longitudinal studies, with some reporting decreases in overall cognitive function while other reported only declines in certain domains or no discernible effect (47, 54, 63, 73, 83, 90). Overall though, a majority of the studies found some predictive association between arterial stiffness and cognitive decline, confirming the conclusions of past studies (47, 54, 63). In addition to examining the association between arterial stiffness and cognitive decline, one study also investigated the effect of pulse wave velocity on development of dementia, finding that it was not predictive of future onset of dementia (54). This result does not necessarily mean that there is no effect, just that it was not statistically significant; this finding makes sense as very few participants in the study were diagnosed with dementia (54). However, patients with both vascular dementia and Alzheimer's disease had higher aortic stiffness in comparison with age-matched controls, meaning that an association may exist in a larger sample of patients (54). Another review article found that across fifteen cross sectional studies, there was a significant association between arterial stiffness and cerebral small vessel disease, as well as between baseline PWV and white matter

hyperintensity volume in the left superior longitudinal fasciculus, meaning that increased arterial stiffness seems to be linked with the development of clinically significant changes in the brain, which are normally seen in patients suffering from dementia, Alzheimer's and other cognitive disorders (29, 83). This finding was supported by another review which found that the white matter hyperintensity volume and number increased along with the number of severe lacunar infarctions from the first to third quartiles when patients were distributed based on pulse wave velocity (29). The review concluded that in hypertensive patients without a history of cardiovascular or cerebrovascular disease, pulse wave velocity is associated with the extent of white matter hyperintensities and the presence of silent lacunar infarctions independent of age, mean arterial pressure, or the incidence of other vascular risk factors (29).

Although the effect of arterial stiffness on cognitive function is agreed upon in the literature, the pathophysiological methods by which changes in vascular function affect these changes is not as clear (63, 83). Cardiovascular factors contributing to the cerebrovasculature include cerebral small vessel disease, neurodegeneration in the brain, cerebral atherosclerosis, and cerebral hypoperfusion and hypoxia (63). Cerebral small vessel diseases include lacunar infarctions, white matter hyperintensities and microinfarctions of the blood-brain barrier and have been associated with cognitive decline (63, 73, 83, 90). In fact, there is a strong association between cognitive deficits and later cerebrovascular disease, suggesting that cognitive impairment may be an ancillary marker of silent brain lesions (63). Stiffening of the arteries and increases in central pulse pressure

result in hemodynamic stress on the heart, kidneys, and brain as previously discussed (63). This stress has the potential to cause structural and functional changes, inadequate perfusion of the tissue and cerebral hypoxia, all predisposing individuals to cognitive decline and dementia, and creating a pathway for the propagation of arterial stiffness to manifest into cognitive decline (63, 73). In fact, previous studies have found that cerebrovascular dysfunction prefaces the onset of cognitive impairment, indicating a role in the developmental mechanisms of dementia (20).

The brain is especially susceptible to structural damage because of its rich vascularization and its low resistance to flow, resulting in high pulsatile stress on the fragile brain tissue (47, 57, 83, 90). The pulsatile flow of blood coupled with the augmented arterial pulse pressure creates a pressure wave into the brain that damages small cerebral vessels, resulting in small arterial disease (29, 47, 54, 83, 90). In particular, small vessel disease has been shown to predominantly affect frontal-subcortical regions that control executive and motor functions, creating a link between arterial stiffness and the deterioration of individual cognitive domains (90). Increased pulsatile flow through the carotid and vertebral arteries proliferate deep into the microvasculature leading to vascular rupture, followed by microhemorrhages, endothelial damage, and thrombotic obstruction (29, 47, 73). Microvascular ischemias in these regions of the brain appear as white matter hyperintensities and small clinically, unrecognizable focal brain infarctions, later causing cognitive impairment and dementia (47). White matter hyperintensities in regions supplying the anterior and middle cerebral arteries have been related to

functional impairments, suggesting a relationship between cerebrovascular pathophysiology, white matter damage, and cognitive function (73). In terms of the exact mechanism leading to the observations seen across many of the studies there is still uncertainty (83). One theory states that the greater arterial stiffness leads to microcirculatory damage via increases in pulsatile pressure and flow load, causing cerebral microvasculature damage despite the blood pressure related protective autoregulatory mechanism (83). Conversely, the other approach says that increased pulsatile load may induce a microvascular remodeling, originally attempting to limit the infiltration of the pressure load on the microcirculatory system by increasing vascular resistance (47, 83). This protective mechanism ultimately becomes disadvantageous as it leads to impaired vasoreactivity and microvascular ischemia (83). While both methods are plausible, the author states, that most likely, it is a combination of these two factors accounting for the link between arterial stiffness and cognitive damage and decline (83).

The link between cardiovascular disease and cognitive impairment leading to decline and eventually dementia comes from the effect of aging on the vascular system. With the structural and functional modifications previously discussed, changes in brain perfusion result in an increased likelihood of cognitive impairment (57). Normal brain perfusion is a complex physiological process, requiring proper function from seven different components: the lungs, the heart, the elastic vessels, the baroreflex, the cerebrovascular arteries, the small cerebral arteries and the cerebrospinal venous system (57). A breakdown in one of these links can cause dysfunction through impaired perfusion of the brain and increase risk of dementia

(57). Reduced cerebral perfusion can lead to the development of ischemic lesions, which act concomitantly with amyloid β-peptide to aggravate the dementia (20). Inadequate cerebral blood flow may also modify amyloid β-peptide transference across the blood-brain barrier, slowing down clearance and promoting accumulation in the brain (20). Lowered cerebral blood flow attenuates cerebral protein synthesis essential for normal cognitive function, leading to impaired cognition (20).

Cognitive Domains:

When attempting to quantify how changes in cognitive function manifest, it is important to understand the various cognitive domains, which regions of the brain govern said domains, and how their function deteriorates with age. As previously discussed, alterations in brain structure and function are closely tied with alterations in cognitive function (21). The basic cognitive functions most susceptible to cognitive decline with age are attention and memory, however as they are each multifaceted, some aspects are resistant while others suffer great decline (21).

Attention is a basic but multifarious process with many subsets, and attention is involved in virtually all other cognitive domains unless the task has become habitual or automatic; therefore, declines in attention have widespread effects (21). There are four divisions of attention, each with unique functions and differing responses to aging. Selective attention is the ability to concentrate on some stimuli while disregarding others that are irrelevant to the task. It is affected by age, as older adults are slower than younger adults with the decline being attributed to a

general slowing of information processing (21). Divided attention is the ability to process two sources of information at once or the performance of two tasks at the same time (21). It is concomitant with significant age-associated decline, especially when the task is complicated, with older adults being more affected by the division of attention (21). The age related decline in this aspect of attention is also explained in terms of dwindling processing resources (21). Sustained attention refers to the ability to maintain concentration over a sustained period of time, and is not impaired by age (21). Overall, older adults show significant impairment in attentional tasks that require dividing or switching between multiple tasks, with relatively stable performance in tasks requiring the selection of relevant stimuli, although they are slightly slower (21). Older adults show the most impairment in memory tasks requiring flexible control of attention, a function located within the frontal lobes (21).

Working memory is a multidimensional cognitive domain that is often cited as a target of age-related deficits in cognitive function (21). While there are several models of working memory, all agree that deficits in working memory come about as a result of a limited capacity system attempting to actively manipulate information held in the short-term memory (21). Older adults experience minimal to no deficit in short term memory, which is the maintenance of a small number of items with rehearsal (21). Manipulating the items in order to repeat them backwards brings in aspects of divided attention, as the original list must be rehearsed while also being manipulated for the new task (21). Previously, working memory was viewed as primarily residing in the prefrontal cortex, but newer

studies also place it in the dorsolateral prefrontal cortex (21). The three theories of decline in working memory are: age related decreases in attentional resources, slowing of information processing speed, and a lack of inhibitory control to filter out irrelevant information (21).

Long term memory is the most well-researched cognitive domain, as many studies are interested in differentiating between age-associated declines and those significant of pathological aging such as dementia or Alzheimer's disease (21). It requires the retrieval of information that is no longer present or being maintained in an active state (21). Similar to attention, memory is a complex domain with some forms suffering drastically from aging while others are relatively constant (21). The subsets of long term memory are: episodic memory for personally experienced events, semantic memory for general knowledge about the world, autobiographical memory, which is a combination of semantic and episodic, procedural memory of specific skills or knowledge, implicit memory, which refers to changes in behavior as a result of previous experience and prospective memory, which is remembering to complete tasks in the future (21). In terms of age-affected decline, episodic memory and prospective memory decline to a significant extent, with all other subsets of long-term memory remaining constant or decreasing slightly (21). Episodic memory involves deficient coding, storage and retrieval of memories that occurred decades ago while prospective memory is often self-initiated with no reminders in the environment (21). While they are not connected, both episodic and prospective memory reside in the prefrontal cortex, an area known to be affected by changes in vascular function and subject to the effects of dementia.

Executive function is a complex system dealing with a variety of different cognitive processes used in planning, organization, coordination, implementation and evaluation of non-routine activities (21). It is the cognitive domain that allocates attentional resources, inhibits distracting stimuli, formulates strategies for encoding and retrieval, and directs activity (21). This functional control center is located in the prefrontal cortex, an immensely important area, but also an area of vascular dementia, and therefore executive function is especially subject to cognitive decline (21).

All in all, cognitive decline does not occur in a predictable pattern. Cognitive domains often age unequally with some aspects being severely affected while others are not affected at all. It appears that the most important factor in determining whether a particular domain will decline is location, as those in the prefrontal cortex receiving turbulent flow seem to suffer the most damage.

Measurement of Cognitive Performance:

Cognitive function can be assessed using measures of functions targeting either global cognition or specific cognitive domains (90). Cognitive function can be measured in a number of different ways. Performance can be evaluated at a single point in time, giving a snapshot of present function, or compared across a period of time giving rate and progression of cognitive decline (90). Global cognitive function is often measured using the Mini Mental State Exam or the Modified Mini Mental State Exam (90). While the Mini Mental State Exam is a very useful test in the assessment of cognitive function, in certain populations it can underrepresent the

amount of cognitive decline (54, 73, 90). The presence of a ceiling effect and the inability of the test to detect small changes in healthy, well-functioning adults may generate results that underrepresent the magnitude of change or are not based on a true baseline (54, 73, 90).

Other studies have reported that cardiovascular mechanisms such as arterial stiffness may impact specific cognitive domains, therefore they can also be tested using targeted tasks (90). These tests are usually more sensitive than a global measure, so they are more likely to pick up either a small change in cognitive function or an association between aortic stiffness and cognitive decline (54). When using specific tests to measure an individual cognitive domain, there can be substantial inconsistencies among the tests used to define each domain, explaining the variability in results (73). Some studies use a single test to define a domain while others use multiple tests, creating questions of whether the intended value was actually fully measured (73).

Tests used to gauge attention range from visual search tasks and Stroop tests for selective attention, to simultaneous task performance to test divided attention and vigilance tasks for sustained attention (21). Tests used to obtain working memory are digit manipulation tasks such as repeating a list of digits backwards (21). Long term memory domain subsets are difficult to test although procedural memory can be somewhat examined through the use of skill tests. Executive function is also harder to test as many assessments involve the use of executive function in successful completion. Specific tests of executive function involve directing attentional processing, decision-making and integration with other

systems in the body (21). An overview of the tests used to measure cognitive function can be seen in Table 2.

Table 2: Overview of how Cognitive Function is Tested.

Cogntive Domain		**Test Type**
Global Cognition		Mini Mental State Exam
		Modified Mini Mental State Exam
Specific Domains	Selective Attention	Visual Search
		Stroop Test
	Divided Attention	Simultaneous Task Test
	Sustained Attention	Vigilance Task
	Working Memory	Digit Manipulation
	Long Term Memory	Skill Tests
	Executive Function	Decision Making

Exercise

Benefits of Aerobic Exercise:

The overall benefits of aerobic exercise are very well known in the risk reduction of chronic diseases and health problems (53, 85). Physical activity is defined as any bodily movement caused by the contraction of skeletal muscle that greatly increases the energy expenditure, which is important in the maintenance of a healthy weight (53). Energy expenditure relates to the frequency, intensity and duration of physical activity (53). Chronic aerobic training favorably modifies traditional risk factors for diseases like blood pressure, plasma lipids, blood glucose, and body composition (69). It also increases aerobic endurance performance and involves large muscle mass groups, leading to an increase in whole body maximal oxygen uptake, enhancing energy expenditure and heart rate (53). Aerobic exercise has also been shown to have anti-inflammatory effects and improve mood and

psychological well being, with acute bouts associated with a reduction in physiological measures of stress and psychological measures of anxiety and depression (69, 81). Both men and women who are physically active have at least 25-35% reduction in relative risk of all-cause mortality, with other studies reporting much higher values (85). An increase in physical activity will decrease the risk of premature death with detraining causing a regression toward the original risk (85). One study reported that the effect of exercise on mortality reduction is graded with even a small improvement in physical fitness associated with a significant reduction of premature death risk (85). For example, an interventional study found that transitioning participants from unfit to fit over five years reduced their risk of death by 44% compared to those who remained unfit (85). Aerobic exercise also decreases the risk of development of Type 2 diabetes, with each increase of 500 kcal per week in energy expenditure associated with a decrease in risk of diabetes development of 6%, and the greatest benefit coming to those who are at highest risk of diabetes (85). Moderate intensity physical activity has been shown to be productive against the development of Type 2 diabetes and a meta-analysis found that modest weight loss through diet and exercise reduced the incidence of disease by 40-60% over 3-4 years (85). In addition to lowering the risk of developing lifestyle diseases such as cardiovascular disease and Type 2 diabetes, physical activity can have a protective effect on the development of colon and breast cancer, with physically active men and women exhibiting a 30-40% lower risk of colon cancer and a 20-30% lower risk of breast cancer, compared to inactive individuals (85). Improvements in psychological well being come through reduced stress,

anxiety and depression and are important in the prevention of cardiovascular and other chronic diseases such as diabetes, osteoporosis, hypertension, obesity, cancer and depression (85). Another important advantage of aerobic training is its effect on Alzheimer's disease and other forms of dementia. In one study of women with mild cognitive impairment, six months of aerobic training was found to lead to an increase in cognitive test scores relative to the stretching control group (5). This finding suggests that aerobic physical activity could be beneficial in patients with all levels of cognitive impairment and that while lifelong exercise is still recommended, beginning physical activity after diagnosis may still serve some benefit.

Aerobic Exercise - Cardiovascular:

Cardiovascular disease is a leading cause of morbidity and mortality in the United States, with estimates that 40% of adults will have one or more form of the disease by the year 2030 (50-52, 68, 69). In order to address this potential epidemic, action needs to be taken. Exercise has long been used for its general health benefits, but more research is being conducted on the potential mechanisms for slowing or reversing the progression of cardiovascular disease such as decreasing the prevalence of hypertension, reducing blood pressure and delaying or preventing age related arterial stiffness (53). Exercise is also used in cardiac rehabilitation clinics with patients suffering from cardiovascular disease, and significantly reduces the incidence of premature death (85). Aging leads to increased risk of cardiovascular disease through two primary mechanisms: stiffening of the large arteries and systemic vascular endothelial dysfunction (50, 68). Regular aerobic exercise has

been shown to prevent or reverse arterial stiffening in adults through arterial remodeling, decreased sympathetic tone, and enhanced endothelial function (51, 53). In order to slow or stop the progression of these two factors, a prescription of aerobic exercise can be used as it has many vasoprotective features.

Recent studies have found that regular endurance aerobic exercise attenuates age-associated reductions in large artery compliance and somewhat restores compliance in previously sedentary middle aged and older adults (50, 70). Middle aged and older men and women who are aerobic endurance exercise trained have lower aortic pulse wave velocities, greater carotid artery compliance and lower systolic arterial blood pressure in comparison with age matched sedentary controls (52, 53, 56, 68-70). In one study involving pre- and post- menopausal women, it was found that maximal oxygen consumption (VO_2 max) was the strongest predictor of arterial stiffness, with an inverse relationship between the variables (70). This finding supported the hypothesis that chronic vigorous aerobic exercise training might slow or even stop the progression of aortic stiffness in the large elastic arteries as there was a significant difference between pre- and post-menopausal sedentary controls but none among the endurance trained groups (69, 70). In a study of male college alumni, vigorous physical activity in the years following college protected against the development of future hypertension with total workload and intensity being inversely associated with risk of disease progression (56). Another study of healthy male participants found that carotid artery compliance declined significantly with age regardless of training status, but the age-associated decline was only about half as great as in endurance trained

individuals (70). In order to eliminate any group differences, another study took an interventional approach, instituting a three-month walking program with previously sedentary middle aged and older males. They found that carotid artery compliance measured using transdermal ultrasound increased by 25% in response to the exercise program, independent of changes in body composition, blood pressure and coronary risk factors (70). These findings indicate that an intervention of moderate aerobic activity can noticeable restore damage to the large elastic arteries seen with age and that a short term program can have similar effects to longer term and more strenuous training plans (52, 69, 70). Acute bouts of aerobic exercise were found to cause an immediate reduction in blood pressure termed post-exercise hypotension, with the greatest decrease seen in patients with hypertension (56). Another study investigated the effect of aerobic training on arterial stiffness in pre-hypertensive and hypertensive subjects (50). Their findings indicated that there was no improvement with aerobic exercise alone, but when training is accompanied by a large decrease in systolic blood pressure or occurs over a prolonged duration, a significant decrease in arterial stiffness results (50). The results of this study found that aerobic training does not necessarily reduce arterial stiffness in pre-hypertensive and hypertensive patients as it does in normotensive patients (50). The authors of the study explained their results by stating that stiffer arteries and impaired baroreflex sensitivity may lead to aerobic exercise-induced peaks of arterial wall stress, possibly exceeding the threshold for beneficial adaptations of arterial compliance (50). In general, any form of exercise

with an aerobic component is associated with lowering large elastic artery stiffness (68, 69).

The mechanisms by which age-associated changes in vascular structure and function lead to stiffening of the vessel and alterations in central hemodynamics are well understood. They involve the remodeling of the extracellular matrix with elastin degradation and collagen deposition as well as the formation of advanced glycation end products, which lead to crosslinking and fluctuations in vascular smooth muscle wall tone (52, 68-70). Studies on these mechanisms in human subjects are somewhat lacking, but there is extensive support for the influence of aerobic exercise altering these pathways involving animal models (68, 69). Following 10-14 weeks of voluntary wheel running in previously sedentary mice, carotid artery stiffness was reduced, however there was no effect on age related elastin deposition (68, 69). A similar study also found that wheel running in mice decreases aortic PWV based on reductions in advanced glycation end products which instigate crosslinking of the proteins in the aorta (68). A third study found that endurance exercise training in rats was associated with increased total elastin content, and 50% less collagen crosslinking in the left ventricle of older endurance trained subjects, suggesting that a partial reversal of age-associated structural changes is plausible following aerobic training intervention (70). Changes in the vascular endothelium are also affected by the aerobic exercise, especially the oxidative stress and inflammatory cascades, resulting in increased bioavailability of nitric oxide (68, 70). Aerobic exercise mitigates the damage caused by age-associated oxidative stress through suppression of the pro-oxidant pathway and

stimulation of the antioxidant pathway (68). Vascular endothelium-dependent vasodilation (nitric oxide bioavailability) is conserved with age in endurance-trained men while it declines rapidly in sedentary age matched controls (52, 70). This augmented bioavailability of nitric oxide could decrease vascular smooth muscle cell tone in the arterial wall, leading to better compliance (70). In fact, regular moderate intensity aerobic exercise restores resting nitric oxide production to young adult levels in previously sedentary older men (69). The mechanism leading to the increased levels of nitric oxide could either be a reduction of endothelin-1, an antagonist to nitric oxide or could be due increased blood velocity induced by exercise. A recent study suggested that mechanical deformation of the endothelium by shear stress increases gene expression of nitric oxide production (53, 56). One study examined the detraining effect 6 months after the cessation of an aerobic training program finding that that the experimental group still had significantly lower PWV values than the baseline values (52). Overall, it appears that improvements in blood pressure measures caused by aerobic exercise are dose related, with greater amounts of exercise leading to greater blood pressure improvement (53).

Previously, it was assumed that the cardiovascular benefits of aerobic exercise were exclusively due to improvements in traditional risk factors such as blood pressure, hyperlipidemia, diabetes mellitus and body composition (68). While all of these factors still apply, it has been proven that modification of these risk factors only accounts for half of the overall effect of aerobic exercise (68, 69). This new theory postulates that aerobic exercise acts in two ways to reduce the overall

risk of cardiovascular disease: lowering traditional risk factors but also creating a protective force against the harmful effects of existing risk factors (68, 69).

Aerobic Exercise - Cognitive:

Recent work exploring the link between physical activity and cognition suggests that there is a link between the two variables, which contrasts the traditional view of the mind as an abstract information processor dissociated from the rest of the body (72). Recent literature reviews have confirmed that there is a strong link between exercise and cognitive function, showing that fitness of the body carries implications for fitness of the mind (72).

As we age, both brain volume and gray matter volume decease leading to impaired function and clinically significant dementia. Exercise has been suggested as a method of slowing this decline, as higher cardiorespiratory fitness is associated with lower rates of age related decline in white and gray matter, particularly in the prefrontal superior parietal and temporal cortices (5, 6). A longitudinal study in cognitively-normal older adults found that participants who exercised three times a week or more were at a lower risk of developing dementia during the six-year follow-up period, independent of any other dementia risk factors (5). Another similar study found that the amount of walking performed by older adults per week was predictive of higher gray matter volume and associated with lower risk of developing mild cognitive impairment or dementia during the nine-year follow-up (5). The benefits of chronic exercise on cardiovascular disease risk have been previously detailed, but this protective factor likely covers the risk of Alzheimer's

disease and dementia (5). The cognitive and cardiovascular systems are heavily intertwined with constant feedback between the two systems, meaning an improvement in one is expected to induce an improvement in the other. In a calculation of population attributable risk, increasing the percentage of the population who are physically active by 25% was the most effective method, including lowering modifiable risk factors, in counteracting the effects of Alzheimer's disease (5). The authors found that implementing this physical activity plan could prevent as many as 230,000 cases of Alzheimer's disease each year in the United States, although this likely underestimates the power of this intervention since physical activity also indirectly modifies other traditional risk factors (5).

During exercise, brain blood flow increases with the volume of change, dependent on the mode and intensity of the activity. During moderate aerobic activity, global brain blood flow increases in parallel with oxygen consumption and cardiac output, potentially improving cognitive function (5, 22). The regional changes in blood flow are due to increased activity of neural networks in the central command and skeletal muscle afferents (5). As a result, the increases in brain blood flow at the beginning stages of exercise are due not only to an increase in cardiac output but also changes in brain metabolism to supply increased neural activation, with cerebral blood flow regulation partially mediating the relationship between aerobic fitness and cognition (5, 22). In aerobically-trained men it was discovered that resting cerebral blood flow velocity was higher at the middle cerebral artery in comparison to sedentary individuals, independent of confounding variables such as blood pressure and body mass index (5). A subsequent study found that

cerebrovascular reactivity in adults of all ages was associated with maximal aerobic capacity, suggesting that function is reduced with age and associated with aerobic fitness (5). An interventional study found that three months of aerobic training led to improved cerebral blood flow in young and older adults, while in a cross sectional study of sedentary and active individuals, fitness and cerebral blood flow regulation showed a positive relationship (22). A study on cerebral blood flow mediating the link between exercise and cognitive function found that responsiveness of the cerebrovasculature was positively linked to cognitive inhibitory control and that habitual physical activity played an important role on the regulation of both (22). Overall, these findings suggest that improved cerebral blood flow regulation could be a pathway through which physical activity influences positive changes in cognitive function (22). In one animal model of exercise effects on cerebral circulation, capillary growth occurred within 30 days of exercise initiation with most of the growth occurring in the motor cortex, while another found that exercise results in higher total surface area of the capillaries in the whole cortex (5, 13). These findings taken together suggest that one possible mechanism of exercise-induced improvement in cerebral blood flow is through angiogenesis, and although these results should translate to human subjects, previous studies have yielded variable results (5, 13). As previously discussed, some individuals have a higher cognitive reserve, giving greater compensatory mechanisms to deal with dementia (5). The physiological explanation of this is that neurogenesis occurs as a result of a stimulating environment. When animals were placed in a stimulating environment without access to physical activity, hippocampal neurogenesis did not occur; in

contrast, those who were given access performed better on learning and memory tests (5). Although studies on neurogenesis have not been performed on human subjects, studies have shown that aerobic exercise is effective in improving memory and cognition, with higher levels of fitness being associated with better performance on cognitive tasks (5). In one of the earlier studies on the topic, older athletes performed substantially better on simple cognitive tests than older sedentary adults, with the older athletes performing at a similar level to young athletes (13). These results can be observed even in childhood with fitter children having cognitive performance similar to young adults and different brain activation patterns, bolstering the idea that physical activity is a modulator of brain structure and function at a young age (5).

Previous studies of the effects of exercise on cognitive function have differed in their cognitive task selection in order to test their specific hypothesis. The speed hypothesis used simple reaction or finger tapping tasks as these are associated with lower level central nervous system function and are less likely to be affected by participant strategies or higher-level cognition (13). The visuospatial hypothesis used visuospatial tasks as researchers proposed that these functions are more susceptible to aging in comparison to verbal tasks (13). In the controlled-processing hypothesis, tasks that involved controlled effortful processing were used as they were suggested to be more sensitive to exercise than automatic processing tasks (13). Finally, the executive-control hypothesis used tasks involving executive function as these tasks do not become automatic over time and require use of areas of the brain shown to be disproportionately sensitive to aging (13). Following a

meta-analysis, it was discovered that exercise had a far greater effect on executive function in comparison with other domains, but any task that involved controlled process showed beneficial increases as a result of the overlap between tasks (13).

In addition to the cognitive benefits of chronic aerobic training, acute bouts of aerobic exercise have been shown to have favorable effects on cognition (72). This theory was first proposed due to the fact that exercise is a stressor that would induce changes in arousal level and an increased ability to inhibit neuronal activity unrelated to task performance, leading to superior stimulus evaluation and cognitive performance (12, 44, 61, 81). It was theorized that there was an inverted-U effect of acute exercise on cognition, with moderate intensity exercise (defined as 40-79% maximum power output or 65-85 maximal heart rate) yielding the best results while high and low intensity both leading to subpar performance (8, 12, 43, 44, 61, 81). This model is theoretical as it is possible for performance at low levels of arousal to be equally good if sufficient attentional resources were allocated; however, during high levels of arousal, neural noise would make it impossible to allocate sufficient resources (44). Intense physical activity at or above the aerobic threshold produces a fatigue state in participants, leading to declines in their cognitive performance, although the effects are transient and have not reached significance in all studies (81). In a recent study it was determined that moderate-intensity exercise with working memory tasks caused a large effect size for speed, demonstrating facilitation and a small effect size for accuracy, signifying a detrimental effect (44). These results would appear to show that a speed-accuracy tradeoff is occurring, although further investigation showed that this was not

occurring as tasks that did not involve speed and accuracy showed similar results for those where a tradeoff was possible (44). The results of a recent meta-analysis studying the effect of acute exercise on speed and accuracy found that the inverted-U hypothesis was supported, with moderate-intensity exercise on speed of processing showing a positive, moderate mean effect size, while high and low intensities demonstrated an effect close to zero (12, 43, 44, 81). Although it was hypothesized that different intensities of exercise would result in variations in accuracy, this was not proven with all three intensities showing effects close to zero (44). Overall, it was determined that acute exercise generated a small but significant mean effect on cognition with speed accounting for a majority of the decline (44). A secondary conclusion echoed that response speed was affected by exercise with faster responses during moderate exercise periods than during rest or low intensity exercise (81). Executive function tasks showed the largest variability with recall and alertness/attention tasks having less (44). The mechanism thought to provoke these changes was augmented brain concentrations of the neurotransmitters dopamine and norepinephrine, which resulted in faster processing speed (44). A second meta-analysis on single bouts of exercise sustaining attention found that contrary to prior studies, acute bouts of physical activity sustain attentional process while sitting resulted in detrimental impairments to the allocation of attentional resources (61). The study also confirmed the dose response curve seen in other meta-analyses with their optimum efficiency achieved with exercise intensities between 65% and 85%, confirming the hypothesis that effect size of cognitive variability is due the type and duration of exercise (61, 81). A study by Sibley and Beilock found that while there

were improvements in the working memory of participants following an acute bout of exercise, only those in the lowest function showed significant improvement (72). This finding suggests that those with lower function, such as aging adults, will acquire the greatest benefit from exercise on working memory while younger adults with good cognitive function may not see any improvement as the exercise only causes maintenance of existing function (72). With respect to duration of exercise, a meta-analysis by Chang et al. found that twenty minutes of exercise was necessary for cognitive benefits with negative effects observed before this criterion (12). This finding supports previous research on duration of exercise for cognitive performance increases and suggests that cognitive activities performed during exercise will improve if tested after the participant has been exercising for an extended period of time (12). All in all, it was concluded that a single bout of aerobic exercise has a positive effect on cognitive performance regardless of when the cognitive task is performed, with variability in the size of the effect based on type, intensity and duration of the exercise (12, 44, 61, 81).

Recently, there have been a small number of studies investigating the relationship between aerobic exercise, improved cardiovascular health and cognitive function. As previously discussed, the aging process leads to a breakdown of the cardiovascular system and a decline in the cognitive system. Aerobic exercise training has been suggested as a protective mechanism in slowing the progression of age-related decline for both of these systems, with a number of studies showing promising results in terms of reduced arterial stiffening or maintenance of cognitive health. Tarumi et al. combined these ideas, investigating whether endurance-trained

individuals had lower central arterial stiffness, and improved cerebral perfusion, hypothesizing that these would lead to superior cognitive function. In their first study, 58 middle-aged participants were enrolled with slightly more women and endurance-trained individuals participating (78). Arterial stiffness measures were collected for all participants, cerebral perfusion was performed on a randomly selected subgroup, and all participants completed a comprehensive neuropsychological assessment (78). From their study, the authors determined that endurance-trained individuals had lower central arterial stiffness and better neurophysiological outcomes in total composite, memory and attention-executive function tasks in comparison with the sedentary individuals (78). In addition, the authors found that cardiorespiratory fitness was positively correlated with higher neuropsychological function and negatively correlated with central arterial stiffness, forming a link between cardiopulmonary fitness, arterial stiffness and cognitive function (78). In the subgroup of participants who had cerebral perfusion measured, occipitoparietal perfusion was greater in endurance-trained individuals and related to lower central arterial stiffness (78). Although there was not a statistically significant relationship between cerebral perfusion and total composite score, there was a strong trend signifying that there may be a relationship between cognitive performance and blood flow (78). In a second study, Tarumi et al. investigated whether a dose-response relationship existed between exercise intensity and cognitive health (79). Master athletes (middle aged and older adults with long-term endurance training) were examined along with sedentary controls (79). In two independent samples, master athletes had higher cognitive performance in memory

and executive function in comparison with sedentary peers (79). Chronic exercise training leads to a reduction in central arterial stiffness, attenuating the blood pressure pulsatility into the brain (79). Arterial stiffening and chronic exposure to high blood pressure pulsatility leads to increased vascular resistance in the cerebral vasculature (79). This unfavorable modification to the cerebrovasculature increases risk of ischemia and impedes the clearance of neuronal waste products, which can eventually lead to clinically significant cognitive impairment (dementia and Alzheimer's disease) (79). Tarumi et al. found that master athletes exhibited greater distensibility of the carotid artery that was positively correlated with higher cerebral perfusion in the occipitoparietal area (79). The last finding from the study was that a dose-dependent relationship exists between exercise intensity and stroke incidence and mortality (79). Moderately active individuals had a 20% lower risk, while highly active individuals had a 27% lower risk in comparison with low-activity individuals. The authors also reported that there currently is no evidence of a dose-response relationship or any other consensus on the optimal exercise dose to slow or prevent the age-associated functional and structural deteriorations to the brain (79).

Benefits of Resistance Exercise:

Resistance exercise training has many benefits for general health not available through chronic aerobic training. It is recommended for athletes of all ages, improves quality of life, induces gains in muscular strength, lean body mass, and greater increases in bone mineral density in comparison with aerobic training

(51, 59, 66). Resistance exercise aims to increase muscular strength and power as well as endurance through static and dynamic exercises though it does not affect VO_2 max (53). It usually occurs over a relatively short period of time with repetitive intense movements involving overloading stimuli as to increase muscle strength and hypertrophy (53). Resistance exercise has also been associated with lower incidence of chronic disease especially diabetes and bone and joint diseases. Resistance exercise has actually been proven to be more beneficial in the control of diabetes through glycemic control than aerobic exercise (85). Resistance exercise is extremely helpful in reducing risk of osteoporosis with increased bone mineral density as a result of regular resistance training and higher bone mineral density in athletes who participated in high-impact sports compared with low-impact sports (85). In addition, routine resistance exercise prevents bone loss associated with aging and significantly reduces the risk and number of falls (85). Finally, resistance exercise throughout the lifetime is associated with improved and preserved musculoskeletal fitness, which is particularly important for maintenance of functional independence (85).

Resistance Exercise - Cardiovascular:

While the cardiovascular effects of aerobic exercise have been thoroughly investigated, less is known about the effects of resistance exercise. Resistance exercise training is associated with increased blood pressure above expected values in some studies but has also been shown to lower blood pressure at a comparable rate to aerobic exercise (51, 53, 56). Due to the discrepancy across studies, more

research is needed; however, resistance exercise performed following the American College of Sports Medicine's (ACSM) guidelines is currently recommended for decreasing blood pressure in normotensive and hypertensive individuals (56, 59). The literature on the effects of resistance exercise on arterial stiffness is somewhat incongruous with some citing no change, while others report an increase and still others finding a decrease (66). This discrepancy could have to do with the mode of exercise completed or length of training and intensity. In a study by Miyachi, it was discovered that high intensity resistance training in young individuals with low baseline levels of stiffness suffered large increases while moderate-intensity older adults had no significant changes in stiffness (48). In order to examine arterial stiffness and blood flow responses following high-intensity resistance training in young and older woman, Rossow et al. conducted an eight-week program (66). Systolic and diastolic blood pressure did not change over time, although it was discovered that older subjects had high blood pressures and higher carotid-femoral PWV, as would be expected (66). Finally, it was discovered that following training PWV mean value did not change in either the young or older subjects (66). In studies where participants solely perform resistance exercise, middle aged and older adults usually have very little change in elastic artery stiffness, and if they do it is a slight elevation compared to sedentary controls, combined with decreases in carotid artery compliance (51, 68, 69). One interesting caveat to this is in middle aged and adult rowers who have reduced arterial stiffness in comparison with sedentary controls and exhibit similar responses as aerobically trained individuals (68). This finding suggests that in a combination of aerobic and resistance training,

the aerobic component may still have the same favorable effects as when performed alone and offsets the effects of resistance training (68, 69). For this reason, resistance and aerobic exercise are often prescribed in tandem as to affect both the cardiovascular and musculoskeletal system positively (51). In one meta-analysis of concurrent training it was observed that PWV decreased a statistically significant amount in the aerobic training group while the concurrent training group did not. Overall, there was no group difference but the reduction in PWV was less apparent and it was hypothesized that the resistance component of the concurrent training limited the improvement in arterial distensibility, supporting previous findings on the effect of resistance training on PWV (51). Concurrent training studies have also found that blood pressure modification is highly dependent on the study protocol with some reporting significant decreases in both diastolic and systolic blood pressure and others finding no effect (53).

The mechanisms by which resistance exercise training improves blood pressure deal with influencing nitric oxide production (53, 56). Chronic exercise training has been shown to decrease production of endothelin-1 (ET-1) a vasoconstrictor peptide produced by vascular endothelial cells, contributing to an increase in bioavailability of nitric oxide and vascular relaxation (53).

In addition to the above-described chronic effects of resistance training, an acute bout of resistance exercise also strongly affects arterial stiffness. A study using one bout of nine upper and lower body resistance exercises found that immediately following and 30 minutes after the exercise bout, carotid arterial compliance and β-stiffness were both significantly different compared to baseline values, with

compliance decreasing and β-stiffness increasing (17). These changes returned to baseline levels by the 60-minute time point, suggesting that the observed change is relatively short-lived (17). The study also found that a single bout of exercise produced an elevation of carotid systolic blood pressure, although the same response was not observed in the brachial systolic blood pressure measurement (17). The authors of the study were unsure of the exact physiological mechanism causing the increase in central arterial stiffness and decrease in central artery compliance, but suggested that they may be a byproduct of corresponding blood pressure changes (17). A second study using male subjects and eight upper and lower body exercises found a significant increase in carotid-femoral PWV 20 minutes after an acute bout of resistance exercise, supporting the conclusions of previous studies (88). Similar to the previous study, the authors were unsure of the exact mechanism of action and offered the same explanation that the observed effects were a byproduct of changes in blood pressure (88). A second proposed explanation for the observed increase in central arterial stiffness was due to the effects of the Valsalva maneuver (88). Performing this maneuver is common during high intensity and maximal intensity resistance exercise, with previous studies showing increases in arterial stiffness. This change in arterial stiffness following the Valsalva is most likely due to increased intrathoracic and intraabdominal pressures, which are then transferred to the aorta and arteries (88). The third possible explanation offered by the authors was that resistance exercise activated the sympathetic nervous system, releasing catecholamine levels, and increasing arterial stiffness (48, 49, 88). A third study compared the effects of an acute bout of aerobic

exercise to an acute bout of resistance exercise, hypothesizing that aerobic exercise would reduce arterial stiffness while resistance exercise would cause an increase in stiffness. Based on previous studies relating baroreceptor sensitivity to arterial stiffness, the authors believed that any change in arterial stiffness following resistance exercise would be due to a change in baroreceptor sensitivity (25). A resistance exercise protocol consisting of three sets of eight upper and lower body exercises was compared to 30 minutes of upright stationary cycling at 65% peak oxygen uptake (25). The authors found that the acute bout of cycling reduced both central and peripheral arterial stiffness while a bout of resistance exercise increased stiffness only, with no effect on peripheral stiffness (25). These findings were supported by previous studies and confirmed that alterations in arterial stiffness are restricted to central elastic arteries with no observable change in peripheral muscular arteries (25). Reductions in baroreceptor sensitivity were observed in both aerobic and resistance exercise with the greatest change associated with the resistance exercise protocol. This variation was attributed to the baroreflex resetting to a higher operating point during resistance exercise in order to include the high blood levels seen during intense resistance exercise (25). The final study examined the effect of single-leg resistance exercise, with the aim of determining whether acute single-leg resistance exercise has an effect on central and peripheral arterial stiffness (24). It was discovered that an acute bout of single-leg resistance exercise decreased arterial stiffness in the exercised leg while there was no effect on stiffness in the contralateral limb or central arteries (24). The novel finding of this study was the reduction in arterial stiffness following the single-leg exercise with no

transfer to the noninvolved limb, as this result is similar to what has been observed with single-leg aerobic exercise (24). The authors proposed vasodilation of the exercising muscle beds as a potential mechanism explaining this acute response (24). Microvessel dilation could have potentially induced a flow-mediated dilation of the larger "feeding" arteries causing sheer stress and prompting the release of nitric oxide from the endothelium (24). While this mechanism may play a role in the decreased arterial stiffness following lower-body resistance exercise, further research is needed to determine the manner in which the many factors affecting arterial stiffness interact.

Resistance Exercise - Cognitive:

The effect of resistance exercise on cognitive function is not fully known, as the literature on the topic is somewhat lacking. Some studies have reported that in comparison with stretching or balance training, resistance exercise provides a greater improvement in perfusion during cognitive tasks (5). Others have seen that in comparison with sedentary controls, those who perform resistance exercise at least once per week have greater perfusion, giving some support to beneficial outcomes from this method (5). Resistance training has been shown to increase insulin-like growth factor 1 in the serum of older adults and can cross the blood-brain barrier resulting in the promotion of neurogenesis in the hippocampus and brain myelination via oligodendrocyte development (6). Following a 52-week study, it was concluded that resistance training once or twice a week had a positive impact on executive function with the benefits persisting even one year after training

cessation (6). The study also found that the twice-weekly resistance training program decreased white matter atrophy at the two year follow-up but had no beneficial effects on gray matter or hippocampal volume (6). Although the quantity of research is improving, there are still questions about the effects of chronic and acute resistance training on cognition, giving increased significance to the present study.

Therefore, as discussed above, cognitive decline and cardiovascular disease are incredibly intertwined. Alterations occur in both the structure and function of the vasculature with increasing age due to a number of different factors. These vascular changes bring about concomitant cognitive decline through an increase in the pulsatility of blood flow to the brain and the accumulation of amyloid β-peptide plaques. The relationship between aerobic exercise, vascular and cognitive health has been widely studied, with exercise having a protective effect on both. This study was conducted in order to investigate what effect of an acute bout of resistance exercise had on vascular and cognitive health.

Methods

Twenty healthy men and women between the ages of 18 and 40, with gender evenly balanced, volunteered to participate in this study. This age range was chosen in order to create a uniform population; as with advancing age, there is an increased prevalence of vascular disease and use of medication to treat vascular dysfunction. Participants were recruited from Syracuse University and the surrounding area. All participants visited the Human Performance Laboratory at Syracuse University on

three separate occasions: the first being an initial screening; the second and third visits serving as the experimental and control visits.

Participants underwent an initial screening to evaluate their overall health, and those with no underlying medical conditions were allowed to partake in the study. Inclusion and exclusion criteria are described in more detail below. The initial visit took approximately an hour to complete, while each of the experimental trials was completed in two hours. During the initial screening visit, participants were informed about the study, given an approximate timeline and then signed a consent form, which was completed prior to the commencement of all other steps. Next, a thorough health history questionnaire was administered asking for information on medications or supplements taken, past history of acute/terminal illness, hypertension, neurological disease, discomfort during exercise, present physical activity state and highest level of education completed. Exclusionary criteria included: Self-reported acute/terminal illness, smoking, hypertension (high blood pressure), diabetes mellitus, hyperlipidemia (high cholesterol), pulmonary disease, renal disease, neurological disease, peripheral artery disease, recent concussions, history of losing consciousness during exercise, and visual impairment preventing successful completion of cognitive tasks.

Following the immediate review of the health history questionnaire, the Montreal Cognitive Assessment (MOCA) was administered. This is a commonly used screening test utilized by health professionals and in research to detect mild cognitive impairment by testing memory, attention, language and executive function. It results in a standardized score representative of clinical cognitive

impairment. This test was crucial to the study because without the ability to quantify that the participant has normal cognitive function, it would not be possible to determine the causation of the change in cognitive function following the acute bout of resistance exercise. A MOCA score of 26 out of 30 was used as the cutoff for normal cognitive functioning.

Following the MOCA, participants were given a more thorough survey of their physical activity called the International Physical Activity Questionnaire (IPAQ), which is a more in-depth way of examining their activity level by intensity. This test has been previously used to assess physical activity and allows for intergroup comparison of MET (Metabolic Equivalent of Task) minutes per week (27, 28). This test was used in the present study as a way to quantify the physical activity levels of all participants.

Following the IPAQ, participant's height was measured using a freestanding stadiometer and weight was measured using an electronic scale. Body composition was measured using air displacement plethysmography in the BodPod (BodPod, Cosmed, Concord, CA, USA). Participants were placed in the chamber, which uses displaced air volume to calculate a person's total body volume. This measure in combination with body weight allows for calculation of percent body fat. During this test, participants were instructed to wear minimal clothing and a swim cap in order to give the best measurement, and dividers were placed around the testing chamber to keep privacy in mind.

Next, the participant's 5 and 10 Repetition Maximums (RM) were determined for bench press and biceps curl. This measure was defined as the maximum amount

of weight that can be lifted using correct form for the specified number of repetitions. Prior to the experimental sets, participants were instructed on proper form and allowed adequate warm-up time in order to keep each participant safe. While determining the participant's maximum, proper form was emphasized and total weight was increased in small increments until the participant was unable to complete the required repetitions. During all weight lifting, a "spotter" was present to ensure safety. The 5RM bench press and 10RM biceps curl values were utilized during the exercise protocol of the experimental condition by performing an exercise routine of five sets of both bench press and biceps curl, with 90 seconds rest in between. If a participant could not complete the full number of repetitions in a set, a "drop set" was used where the weight was lowered until the participant could complete the required repetitions. This protocol has been previously used in this lab to incite increases in arterial stiffness (4, 41, 42).

Finally, participants were familiarized with the cognitive tests (Memory, Flanker, Working Memory) used in the experimental trials in order to lessen the learning effect. Participants were scheduled for both the second and third appointments following the first visit, with at least 24 hours minimum between visits.

For the exercise and non-exercise time control conditions, participants were tested in the postprandial state (at least three hours fasted) and asked to refrain from caffeine ingestion and any physical activity more strenuous than walking before their visit, in order to eliminate any outside influences on blood pressure and to be sure that any changes observed were attributable to interventions of the

present study. Participants were also asked to refrain from taking any medications or dietary supplements prior to coming into the lab as some of these have been shown to have hemodynamic effects. Test order was counterbalanced with participants being randomly placed into two groups; one group performing the exercise trial on their second visit followed by the non-exercise trial on the third and the other group doing the opposite in order to remove any influence of task order on the results of the present study. Figure 11, located in the Appendix, shows the timeline for each visit.

Upon arrival to their appointment, participants first were given Trails A, Trails B, Digit Substitution and Verbal Fluency tests. The Trails A and B tests are executive function tasks and required participants to draw a path between circles with digits inside. Trails A consisted only of numbers and the task was to connect all of the circles in numerical order as fast as possible. Trails B had both numbers and letters and a similar goal, although alternating between numbers and letters (ex: 1-A-2-B-3-C). The digit substitution task, an executive function and memory test, required participants to place symbols assigned to the numbers 1-9 into empty boxes. There was no pattern associated with the order of the digits in the test so participants were required to memorize the symbols in order to successfully complete the task. In the verbal fluency task, an executive function test, participants were asked to name as many words starting with a given letter as possible. The letter was a random constant with no repetition across the four administrations of the test. These tests were recorded for time or number completed, and gave

valuable data about the cognitive domains, specifically memory and executive function.

Next, participants underwent resting vascular measures followed by three computer cognitive assessment tests. Blood pressure and arterial stiffness were measured using the Mobil-O-Graph (Mobil-O-Graph PWA, Stolberg, Germany), an automated oscillometric device that has been used previously in this lab and validated against invasive clinically relevant measures (62, 86). From this device, it was possible to measure pulse wave velocity (a measure of arterial stiffness), augmentation index (a measure of increase in SBP caused by reflected wave, AP/PP), augmentation index at 75 beats per minute (augmentation index normalized for a heart rate of 75 bpm), stroke volume (amount of blood pumped out of heart during each cardiac cycle, CO/HR), heart rate (number of beats per minute), cardiac output (volume of blood pumped per unit time SV/HR), cardiac index (heart performance relative to the size of an individual CO/BSA) and total peripheral resistance (impedance to blood flow through small vessels, MAP/CO). In addition, central and peripheral systolic blood pressure (pressure when heart beats), central and peripheral diastolic blood pressure (pressure when heart relaxes), mean arterial pressure (average pressure), central and peripheral pulse pressure (SBP minus DBP) were calculated using the blood pressure device. P1 (first systolic inflection), P2 (systolic peak), Pb (backward wave pressure), Pf (forward wave pressure), reflection magnitude (Pb/Pf x 100) and augmentation pressure (difference between second and first systolic peak) were calculated using wave separation analysis. The cuff and instrument are almost identical to one used during

a doctor's office visit, except that they are able to get more complex measures of the cardiovascular system. This measure was taken a total of two times during the visit (one pre-condition and one immediately following exercise/control) in order to get a better understanding of how cardiovascular function varies during strenuous cognitive activities.

The computer-based cognitive tests consisted of a memory task, a working memory task and an executive function task. The total time was approximately twenty minutes from start to finish with two trials of the working memory and executive function tasks and one trial of the memory task. The memory task was a delayed recall where participants were asked to categorize a list of words. The study list or "old words" were shown at the beginning of the testing session; new words were added in later during the memory test trial designed to act as distractors. Participants were asked to think back to the list of words that they saw at the beginning of the test and distinguish whether the presented word belonged to the old or new category. The working memory task consisted of an N-back task or 2-back task. Participants were presented with a series of numbers on the screen one at a time. They were instructed to press the right button to respond when the number presently on the screen matched the number that was shown two previously. The executive function task was a Flanker test where participants were presented with five arrows. The target arrow was always in the center, but it was flanked by two different patterns, congruous (>>>>>) or incongruous (>><>>). The task was to identify the direction of the target arrow and push the button that pointed in the same direction. Responses to all tasks were entered using a two-

button clicker. These tasks were completed twice per visit, once before and once after the exercise/control condition. All computerized tasks were performed while in the supine position on a specialized television that was suspended horizontally above the participant's head.

The maximum amount of weight that a person is able to lift with proper form for five repetitions on the bench press and ten repetitions for the biceps curl determined during the first visit was used during the exercise protocol for the present study. Five and ten repetition maximum tests are often used in strength assessment and have been proven as a safe way to assess strength. During the initial visit, participants completed one set at a submaximal load with their 5RM and 10RM extrapolated using standardized prediction table from the National Strength and Conditioning Association. The suggested weight was added until participants were unable to complete the required repetitions. Prior to the experimental repetitions, participants were allowed one set of ten on the bench press to warm up. The exercise condition in the study consisted of five sets of the participant's 5RM bench press and five sets of their 10RM biceps curl. Bench press was conducted using a standard 45-pound Olympic bar and biceps curl was completed using a two-handed curl bar. These sets were completed following the first round of cognitive testing. Rest between each set was set at 90 seconds and kept consistent for all participants. Between sets, the difficulty of the previous set was discussed on a rating of perceived exertion (RPE) scale of 1-10. Workload was adjusted based on the RPE scale as to maintain each set at a strenuous intensity. If participants were unable to complete a full set, a "drop set" protocol was used where weight was lowered in

small increments until they were able to successfully finish the set. During all lifting sessions, a "spotter" was present for the safety of the participant. This protocol has been previously used to induce acute vascular changes such as increases in aortic pulse wave velocity and carotid pulse pressure (4, 41, 42).

The non-exercise control used in this study was a 35-minute documentary on the Solar System ("Wonders of the Universe", BBC). It was selected as an emotionally neutral, non-exercise time control for the resistance exercise. Participants sat quietly in a calm environment and watched the film using headphones to eliminate distraction. The duration of the non-exercise control was used in order to be a time-matched control to the exercise protocol. Similar protocols have been used in prior studies as a non-exercise time control (61).

Following the completion of the exercise/control condition, participants returned to the examination bed for a period of recovery. The recovery period was set at ten minutes for the exercise protocol and five minutes for the control. This recovery period was incorporated into the protocol in order to allow acute local blood flow regulation to normalize as taking blood pressure measures immediately following resistance exercise was found to be extremely painful for the participant and as it was in line with other studies measuring cognition following exercise. Following the prescribed rest period, another vascular measure was taken followed by the three previously described computerized cognitive tests. Test order was reversed so that the effect of task order could be eliminated. A new study list was also used so that results on the memory test could be isolated as occurring following

the intervention. Following the completion of all computerized tests, the visit was concluded with the four paper and pencil tests.

Vascular measures were taken two times during each visit to the laboratory, as described previously, using the Mobil-O-Graph automated oscillometric brachial blood pressure device. This device has been previously validated against both invasive and noninvasive measures of central systolic blood pressure (62, 86). The device consists of a standard blood pressure cuff placed over the brachial artery, and then attached to the measuring unit. Vascular measures were recorded approximately half way through the working memory and executive function tasks and 45 seconds into the memory task. The times were chosen in order to allow the participant to become engaged with the test so that when the measure was taken it would not be as disruptive.

Statistical Analysis:

Statistical analyses were performed using SPSS version 23.0 (IBM, Chicago, IL, USA). Data is expressed as mean ± standard deviation. Data were analyzed using a 2x2 analysis of variance (ANOVA) with repeated measures [(RE vs. Non-exercise time control) x (pre vs. post)]. If a condition by time interactions was detected, appropriate post hoc comparisons were made using t-tests with a Bonferroni correction for multiple comparisons. Statistical significance was set *a priori* as $p<0.05$.

Results

Participant Characteristics:

Twenty participants were recruited for the present study with gender equally balanced. Table 3 shows the mean and standard deviations for selected descriptive variables. All participants fell within the age range of 18-22, as they were all current undergraduate students at Syracuse University. Average Montreal Cognitive Assessment score is presented in Table 3 with all participants scoring at least a 26 on the test, signifying a good cognitive health at baseline (range 26-30). BMI data is presented in Table 3 with the average falling within the normal weight category (range 20.3 to 34.9 kg/m^2). Bench press and biceps curl strength varied greatly among participants with values ranging from 20.4 kg to 111.1 kg for the bench press and 11.3 kg to 38.5 kg for the biceps curl. Male participants lifted a significantly greater amount relative to body weight (weight lifted in kg/ body weight in kg) in comparison with female participants ($p<0.01$). The study cohort consisted of thirteen White/Caucasian individuals, one individual of Caucasian and South American descent, three White/Hispanic individuals, one Black/African American individual, one individual of White and Asian descent and one Caribbean Islander, all according to participant self-reporting. All participants were highly educated with all reporting completion of some college.

Hemodynamics:

Hemodynamic data is presented in Table 4. No significant differences were observed between resistance exercise and the non-exercise time control (sitting) at

pre-condition across any variable ($p>0.05$). Brachial SBP, and MAP increased slightly, while DBP decreased slightly following resistance exercise, however none of these changes were statistically significant ($p>0.05$). There was a condition by time interaction for peripheral PP ($p<0.05$). This interaction was driven by a significant 29.8% increase in peripheral PP following resistance exercise ($p<0.05$) with no change in peripheral PP following the non-exercise time control ($p>0.05$). Heart rate displayed a significant interaction between conditions ($p<0.05$). This was driven by a significant 17.2% increase in HR following resistance exercise ($p<0.05$) with no change in HR following the non-exercise time control ($p>0.05$). There were condition by time interactions for cSBP and cPP ($p<0.05$). These interactions were driven by significant 13.0% and 51.4% increases in cSBP and cPP respectively following resistance exercise ($p<0.05$) with no change in cSBP and cPP following the non-exercise time control ($p>0.05$). A graphical representation of the difference in cPP can be seen in Figure 12. There was a condition by time interaction for RM ($p<0.05$). This interaction was driven by a significant 13.3% increase in RM following resistance exercise ($p<0.05$) with no change in RM following the non-exercise time control ($p>0.05$).

There was a condition by time interaction for P2 ($p<0.05$). This interaction was driven by a significant 13.0% increase in P2 following resistance exercise ($p<0.05$) with no change in P2 following the non-exercise time control ($p>0.05$). There was a condition by time interaction for both Pb and Pf ($p<0.05$). These interactions were driven by significant 58.3% and 36.3% increases in Pb and Pf respectively following resistance exercise ($p<0.05$) with no change in Pb and Pf

following the non-exercise time control ($p>0.05$). Graphical representations of the difference in Pb and Pf can be seen in Figures 14 and 15 respectively. There was a condition by time interaction for P1-cDBP ($p<0.05$). This interaction was driven by a significant 44.8% increase in P1-cDBP following resistance exercise ($p<0.05$) with no change in P1-cDBP following the non-exercise time control ($p>0.05$).

There was a condition by time interaction for PWV ($p<0.05$). This interaction was driven by a significant 10.2% increase in PWV following resistance exercise ($p<0.05$) with no change in PWV following the non-exercise time control ($p>0.05$). A graphical representation of the difference in PWV can be seen in Figure 13.

Cognitive:

Cognitive performance data is presented in Tables 5 and 6. No significant differences were observed between conditions at the pre-condition time point across any variable ($p>0.05$). There were no significant condition by time interactions for the N-back or Word Recognition tasks ($p>0.05$). There were condition by time interactions for congruent and incongruent average reaction times for correct answers ($p<0.05$). These interactions were driven by a significant decrease in congruent and incongruent reaction times following resistance exercise ($p<0.05$) with no change in congruent and incongruent reaction times following the non-exercise control (sitting) ($p>0.05$). There were no other significant condition by time interactions for the Flanker task ($p>0.05$). There were no significant condition by time interactions for any of the trail making, word naming or digit substitution tasks ($p>0.05$).

Discussion

Summary:

High blood pressure and other cardiovascular diseases are extremely prevalent worldwide, with numerous detrimental side effects coming about as a result. One potentially detrimental consequence of CVD and related vascular sequela is cognitive dysfunction. Aging and CVD contribute to increases in arterial stiffness, which may detrimentally impact cognitive performance. The present study set out to investigate the effect of an acute bout of resistance exercise on vascular and cognitive health. The results of the present study can be summarized as follows: 1) Peripheral and central pulse pressure along with central systolic blood pressure increased following the resistance exercise condition despite insignificant changes in brachial systolic, diastolic and mean arterial pressures; 2) Augmentation Index, Pb, Pf and Pulse Wave Velocity also increased following acute RE; 3) Changes in cognitive performance were somewhat less noticeable, with the only significant changes being faster reaction times for select attention tasks following acute RE. This means that pressure from wave reflections, central blood pressures and central arterial stiffness increased while cognitive function remained largely unaffected. Taken together, these results suggest that in young, healthy adults, increases in arterial stiffness and pulsatile blood pressure stemming from an acute bout of resistance exercise may not have a detrimental effect on cognitive function.

Hemodynamics:

The most notable outcome from the present study confirmed the findings of previous literature on the effect of acute resistance on central arterial stiffness (26, 41, 88). Following one acute bout and a resting period of ten minutes, central arterial stiffness was significantly higher compared to the pre-condition time point with no change in peripheral arterial stiffness. This finding has been previously shown in many other acute resistance exercise studies (14, 17, 25, 41, 88), although this finding is not unanimous (42); and whether the effect remains with resistance exercise training is still unknown (49, 66). In studies that measured the length of the effect on central arterial stiffness, it appeared to continue for between 20 and 60 minutes (14, 17, 41, 88). In addition, two studies found increases in peripheral arterial stiffness without simultaneous increases in central arterial stiffness (4, 24). Although this would appear to contradict the findings of the present study, in both cases the experimental design differed significantly from the present study. Heffernan et al. found that in single-leg resistance exercise, the bout of activity decreased the arterial stiffness in the exercised leg with no change in stiffness of the contralateral leg or central arteries (24). This finding was consistent with previous literature and further expounds that there is a difference in both the modality of exercise, the specific exercises chosen and the vascular bed assessed (i.e. central vs. peripheral) (24). In a study by Augustine et al., they investigated the effect of consuming a high-fat meal before engaging in resistance exercise (4). The study concluded that consuming a high-fat meal had no effect on central arterial stiffness, but a high-fat meal followed by resistance exercise lead to a decrease in PWV,

indicating that there are a number of factors that affect central arterial stiffness (4). Overall, a general consensus has been reached that an acute bout of upper body resistance exercise causes an increase in central arterial stiffness without a perceptible effect to peripheral vasculature. Central arterial stiffness is critical to overall and cardiovascular health due to the role of the aorta as the principle artery within the body. An increase in stiffness within the aorta sends highly pulsatile flow to every vital organ system within the body, leaving them vulnerable for damage.

The central pressure wave is the summation of two pressure waves: the forward wave generated with each cardiac cycle and the reflected wave initiated when the forward wave hits the aortic bifurcation. In order to assess wave reflections, one method is to separate the single wave into its components. Pressure of the forward wave (Pf) and pressure of the reflected wave (Pb) both increased significantly following an acute bout of resistance exercise. These findings were somewhat supported, with previous studies discovering a significant increase in Pf, but no significant change in Pb (41, 42). A second method used to assess wave reflections is reflection magnitude, calculated as the ratio of Pb height to Pf height expressed as a percentage (71). In the present study, it was observed that reflection magnitude increased significantly following the acute bout of resistance exercise, confirming that resistance exercise increases wave reflection magnitude, suggesting that as a result of the stiffer vessels and increased pulse wave velocity, the blood pressure wave reaches the aortic bifurcation faster, causing a greater reflected wave and placing an increased load on the heart during systole (26, 70).

In the present study, there were no significant changes to brachial systolic, diastolic or mean arterial pressures, while peripheral and central pulse pressure and central systolic blood pressure all increased significantly following resistance exercise. The increase in central pulse and systolic blood pressures is important because they indicate an increase in the force of the blood pressure wave leaving the left ventricle. This finding of increased central systolic blood pressure was supported by studies on the acute effect of resistance exercise on hemodynamic measures, which found no increases in brachial systolic blood pressure, but a significant increase in central systolic blood pressure (17, 41, 42). This would suggest that the magnitude of changes in systolic pressure might not be fully appreciated by a brachial measurement alone and that when attempting to evaluate the effect of acute resistance exercise on the vessels, a central measure should be used (17, 88). Previous studies have also found that following an acute bout of resistance exercise, central and peripheral diastolic blood pressures are unaffected, supporting the findings of the present study (24, 25, 49, 66, 88); however, this conclusion is not universal, with others reporting significant changes in brachial and central diastolic blood pressure post exercise (41, 42). The change to central and peripheral pulse pressures following resistance exercise is a somewhat debated topic, with some studies reporting no significant changes (88) and others finding a statistically significant change, consistent with the present study (17, 41, 42). All in all, the above changes taken together would suggest that an increase in aortic stiffness leads to an increase in pulse wave velocity, shortening the time to when the blood hits the aortic bifurcation and increasing the magnitude of wave reflections.

This augmented reflected wave increases central pulse pressure and leads to increased strain on the heart during systole.

In this study, heart rate increased following the bout of acute resistance exercise, confirming the work of previous studies (14, 17, 24, 41, 42, 88); although, when an individual becomes resistance-exercise trained, there is no alteration in resting heart rate (49, 66). An increase in heart rate along with concurrent increases in arterial stiffness cause greater wave reflections due to the fact that cardiac output increases, meaning that more blood is flowing toward the aortic bifurcation at a higher velocity due aortic stiffness, causing greater wave reflection magnitude.

The mechanisms by which acute bouts of resistance exercise lead to alterations in hemodynamic function are not yet well understood, but there are a number of theories that may help to explicate the interconnected nature of the observed changes (17, 48, 88). First, it has been shown that acute bouts of resistance exercise lead to increases in central systolic and pulse pressures (17, 88). Yoon et al. and DeVan et al. hypothesized that changes in arterial stiffness after aerobic and resistance exercise are assumed to come about as a result of fluctuations in blood pressure (17, 88). Aerobic exercise uses large muscle groups in a rhythmic pattern, so blood pressure changes very little (88). Contrastingly, resistance exercise has been shown to cause vast increases in blood pressure, up to 310/250 mmHg, during exercise (25, 48, 88). Long-term exposure to resistance exercise brings about increased smooth muscle content of the vessel wall and changes in the load-bearing properties of elastin and collagen, explaining the

pathophysiological role of resistance exercise on increased arterial stiffness (48, 88).

Yoon et al. also proposed a second mechanism for the observed increase in arterial stiffness following acute resistance exercise as the effects of the Valsalva maneuver during exercise (88). This technique utilized during high and maximum-intensity resistance exercise leads to increases in central arterial stiffness when performed deliberately (88). Increased stiffness is most likely caused by increased intrathoracic and intraabdominal pressures, as this force is then transferred to the aorta and large arteries (88).

The third mechanism proposed by Yoon et al. suggested that performance of resistance exercise elevates catecholamine levels and stimulates the sympathetic nervous system (48, 88). This causes an imbalance in the autonomic nervous system through increased sympathetic activation and decreased parasympathetic activation, leading to increased arterial stiffness by applying constant strain on the vessel wall through vasoconstriction (25, 88). Increased heart rate following resistance exercise has been previously used as an indicator of increased sympathetic activity, supporting the findings of the present study (42).

The final mechanism from Yoon et al. referenced a study by Heffernan et al. stating that the sensitivity of carotid baroreceptors may play a role in increasing arterial stiffness following resistance exercise (88). The study by Heffernan et al. compared changes in baroreceptor sensitivity following aerobic exercise in comparison to resistance exercise (25, 88). It was observed that both aerobic and resistance exercise lowered baroreceptor sensitivity, with the bigger change and

increases in arterial stiffness following resistance exercise (25, 88). It was hypothesized that baroreflex sensitivity was altered by increases in blood pressure of the vessels housing the baro-sensory regions (25). This decrease in sensitivity could result in depressed mechanotransduction, reduced baroreceptor afferent firing, less inhibition of sympathetic outflow, and diminished amplification of vagal tone (25). It was also hypothesized that baroreflex sensitivity during resistance exercise may be rapidly reset to a higher operating point in comparison with aerobic exercise, reducing sensitivity in order to include the previously mentioned extreme escalation of blood pressure (25). A study by Collier et al. suggested that acute exercise-induced changes in arterial distensibility and vasodilation are disassociated, and that changes in arterial function are unlikely to be a mechanism for alterations in arterial distensibility after exercise (14). They also noted that the increase in vasodilation might be a compensatory reaction to the increase in arterial stiffness following an acute bout of resistance exercise (14).

The hemodynamic changes seen in the present study confirm those of previous studies on acute resistance exercise induced changes in vascular structure and function. Increases in arterial stiffness were brought about by larger forward and backward pressure waves, altering the way the waves intersect. The changes in central stiffness are thought to occur as a result of fluctuations in blood pressure, and eventually lead to detrimental pulsatile blood flow traveling to the kidneys, brain and other high-flow, low-resistance, target end organs. Sensitive tissues, especially in the brain, become damaged as a result of the highly pulsatile flow, leading to theoretical cognitive impairment.

Effect of Resistance Exercise on Cognitive Function:

Current literature examining the effect of resistance exercise on cognitive function is somewhat limited, with a great deal of uncertainty surrounding this very important issue. According to Chang et al., cognitive performance is divided into four main categories: speed, visuospatial, controlled and executive control (11). The present study found that an acute bout of resistance exercise had very little impact on overall cognitive function in comparison to a non-exercise time control, with slight but significant improvements in reaction times for the attention task.

Executive function/attention measured using the Flanker task showed significant improvement in the present study for congruent and incongruent correct reaction times, while accuracy remained consistent. While the style of Flanker task Tsai et al. used in their study varied slightly from that of the previous study, the findings of the two studies were very similar (82). Both moderate-intensity and high-intensity acute resistance exercise led to improvements in reaction time of congruent and incongruent Flanker tasks (82). Tsai et al. also found that accuracy increased significantly for the incongruent tasks following moderate and high intensity exercise, although this result needs to be carefully considered due to the fact that a ceiling effect may be present (82). In the present study, there was no significant change in accuracy, contradicting the results of the aforementioned study.

In terms of working memory, measured using the N-back test in the present study, there was no significant improvement was seen in the reaction time for a correct response. This finding would suggest that following acute resistance

exercise, executive function is not able to better control attentional resources, allowing for recognition of target stimuli and the filtering out of distractors. This finding was supported by Pontifex et al., who found that aerobic exercise had a positive impact on reaction time both immediately and 30 minutes post intervention, although this did not apply to resistance exercise (60). While the present study did not compare post-exercise cognitive function between modalities, there is certainly a difference in response between acute aerobic and resistance activity, explaining the difference in control of executive function (60). A second study used five variations of the Stroop test to determine whether general or selective improvements in cognitive function could be brought about following a bout of acute resistance exercise (11). They found that exercise improved reaction times across all five tests, with the authors suggesting that this may be interpreted as a sign of general improvements in cognitive function (11). While the Stroop test does involve the use of multiple cognitive domains, there were a number of cognitive domains unaddressed in the aforementioned study, so it may not yet be suitable to conclude that overall cognitive function increases as a result of acute resistance exercise. In addition, the findings of the Chang et al. study refute both those of the present study and a study comparing the effects of aerobic and resistance exercise, which used a more robust cognitive protocol and therefore would be more suitable to judge improvements in overall cognitive function (60). A third study by Lachman et al. found that in a six-month home-based resistance exercise study, there were no significant differences in working memory between the experimental and control groups, but a larger increase in resistance across the

program was significantly associated with a positive change in working memory performance (38, 84). The study used the Wechsler Adult Intelligence Scale backward digit span, a test very similar to that of the previous study, as subjects are asked to memorize and manipulate strings of numbers presented to them (38). This result signifies that resistance training may be beneficial for working memory task performance when task intensity is monitored and progressed but, unfortunately, it is unknown whether this pattern is a result of training or appears after acute resistance exercise. Therefore, these results cannot be compared to those of the present study because the intensity of the exercise performed in the present was not varied.

Finally, a fourth study investigating the relationship between acute bouts of exercise (resistance and aerobic) and executive function found that both types of exercise led to improvements in Stroop test performance, but had no effect on the trail-making task (2). This conclusion was supported by the present study, which also conducted the trail-making task, finding that there was no change following either the control or experimental condition (2). This result along with previous literature on the topic, suggests that improvements in executive function as a result of acute exercise may be task dependent, with even aerobic exercise having no effect in some instances.

The literature studying the acute effects of resistance exercise on memory is severely lacking, and to our knowledge, this is the first study examining the effect of acute resistance exercise on short-term memory. The present study found that there was no significant decrease in the number and overall percentage of false alarms.

This finding would suggest that an acute bout of resistance exercise would not improve the accuracy of short-term memory and would maintain reaction speed.

The mechanisms by which acute bouts of resistance exercise influence cognitive function is still not yet well understood, although there are a plethora of promising theories. The first proposed mechanism is the relationship between secreted levels of biomarkers like cortisol, growth hormone and insulin-like growth factor 1 and exercise intensity (82). Cortisol, produced by the adrenal cortex, is released in response to a stressor and leads to increases in arousal, which will be discussed in more detail later (82). Increased cortisol levels could result in dysfunction of neuroplasticity and neurogenesis of the hippocampus since steroids inhibit glucose transport in the hippocampal neurons and glia, the location of executive function along with the frontal lobe (82). According to the aforementioned inverted U-shaped curve, moderate-intensity exercise causes the greatest positive effects on cognitive performance (8, 11, 43, 44, 61, 81). A similarly shaped curve exists for cortisol levels, with moderate levels being correlated with the highest cognitive function, and higher values interfering with hippocampal and prefrontal function (82). Therefore, it would appear that moderate-intensity exercise bringing about a moderate level of cortisol secretion would be optimal for cognitive function. In the present study, the exercise program was designed to be of moderate-intensity, therefore it is possible that the lack of decline in cognitive function following acute resistance exercise could be due to the beneficial effects of cortisol on cognitive function.

Two other secreted biomarkers important in the relationship between resistance exercise and cognition are growth hormone (GH) and insulin-like growth factor 1 (IGF-1) (11, 38, 82, 84). This relationship is most likely due to the fact that these signaling peptides can cross the brain-blood barrier, binding to receptors in the central nervous system, affecting growth of glial cells, myelination and neurons (36, 82, 84). Previous studies have demonstrated that serum IGF-1, and GH levels are associated with behavioral performance (information processing speed, target detection and short term memory), and that acute resistance exercise positively augments these levels (11, 36-38, 82, 84). In addition, animal models have shown that IGF-1 is essential in stimulating angiogenesis in the brain through the regulation of vascular endothelial growth factor (VEGF) (30). Improvements in cognitive function could be due to this hormone cascade, as newly-proliferated cells need nourishment to thrive, but it is more likely to play a role over a longer period of time rather than as a result of an acute bout (30). Another possible explanation of the lack of decline in cognitive function following acute resistance exercise could be due to the beneficial effects of GH, IGF-1 and VEGF on cognitive function.

Brain derived neurotrophic factor (BDNF) is a fundamental protein in regulating preservation, development and survival of neurons, and influences learning and memory (1, 18, 30, 58, 64, 87). Exercise induces increases in BDNF levels in the hippocampus, triggering neurogenesis (1, 37, 60). Previous studies have reported improvements in Stroop test scores following acute bouts of exercise, with the finding being correlated to increases in BDNF levels (18). There is also evidence that aged brain tissue responds favorably to BDNF and that reduced

expression of BDNF may underlie age-related deficits in long-term potentiation, a cellular model of memory, learning, memory and hippocampal function (30, 37). Therefore, exercise induced surges of BDNF could be a powerful implement in combatting degenerative neuromuscular disorders and diseases affecting cognition brought about by a sedentary lifestyle (1, 18, 30). Whether or not resistance exercise can stimulate the release of BDNF is still up for debate, with some studies suggesting that resistance exercise can lead to increases (1, 87), others finding that aerobic exercise alone has the ability (1, 18, 84), and still others noting that exercise modality does not matter as long as the participants are familiar with the task (64). A recent study found that contrary to past work, resistance exercise performed as an acute bout or as part of prolonged training can cause increases in BDNF secretion levels equal to that of endurance exercise (87). Therefore in the present study, it is plausible to suggest that the acute bout of resistance exercise may have triggered the release of BDNF, explaining the absence of decline in cognitive function. In addition, it has also been suggested that BDNF is used in the regulation of neurotransmitters such as dopamine, and that it may play a role in the exercise-induced effects of neurotransmitters (37).

Previous studies have also pointed to the Arousal Theory when theorizing mechanisms for resistance exercise induced improvements in cognitive function (11). The Arousal Theory views exercise as a stressor, with increasing intensity leading to amplified arousal level (3, 43). Cognitive performance is dependent on the proper allocation of resources to meet task demands, and acute exercise alters how these resources are distributed (39). As exercise intensity increases, it brings

about a greater arousal level, which has been shown to increase cognitive performance. In addition, one study found that with increasing arousal level as a result of exercise, narrowing of the visual field occurred, suggesting that attention is focused on the central portion of vision, allowing distractor stimuli to be ignored (3). Maximal cognitive performance occurs with intermediate intensity exercise, as explained by the aforementioned inverted U-shaped curve (8, 11, 39, 43, 44, 61, 81). This theoretical curve was confirmed through a meta-analysis by McMorris et al., where they found that intermediate intensity exercise improved reaction times in a working memory task (43). McMorris et al. theorized that changes in arousal leading to improvements in reaction times had to do with the interaction between the neurologic and endocrine systems (43). Prior to, and during exercise, the sympathoadrenal system becomes activated, releasing catecholamines, epinephrine, norepinephrine and dopamine into the blood (43). Changes in arousal have previously been measured through increases in heart rate and catecholamine levels, with previous studies finding that an increase in catecholamine levels induced by exercise are associated with greater learning ability (11). Therefore, a reasonable relationship exists between moderate intensity exercise and improvements in cognitive function. Since the exercise used in the present study was of moderate-intensity, the lack of decline in cognitive function could also be explained by an optimal level of arousal allowing for attentional resources to be allocated to the cognitive task and the filtering out of distractor stimuli.

Blood flow to the brain has also been previously investigated as a mechanism through which acute bouts of exercise can stimulate improvements in cognitive

function (2, 60). Moderate intensity aerobic activity has been shown to increase cerebral blood flow, while resistance exercise has been shown to decrease blood flow and oxygen consumption (at least systemically) (2, 60). Given the vastly different metabolic response to aerobic and resistance exercise, it is possible that resistance exercise affects cerebral function differently than aerobic exercise (60). Recent animal model studies have found that these increases in cerebral blood flow do not occur universally across the brain, but rather are localized to areas involved with locomotion, equilibrium, cardiorespiratory function and regions of the hippocampus, leading to the possibility that the acute resistance exercise performed in the present study may have lead to regional increases in cerebral perfusion and prevented declines in cognitive function (60).

Resistance Exercise, Arterial Stiffness, and Cognitive Function:

The present study was designed to measure the effect of resistance exercise mediated arterial stiffness on cognitive function. As previously discussed, advancing age leads to the stiffening of the arteries through a number of different mechanisms, such as decreases in nitric oxide bioavailability, the degradation of elastin fibers, and the deposition of collagen into the tunica media (15, 23, 67, 76). This change in the distensibility of the arteries has been shown to have detrimental effects on cognitive function through target end organ damage (16, 34, 86). One of the organs most affected by the highly pulsatile flow from the stiffer arteries is the brain (9, 33). This is due to its rich vascularization and low impedance of flow, resulting in extremely high pulsatile stress on the fragile brain tissue (47, 57, 83, 90). Increases

in high-pressure flow through neural tissue lead to damage, such as microhemorrhages and microvascular ischemia, which appear as white matter hyperintensities (29, 47, 73). These injuries to the brain have a detrimental effect on overall neural tissue health and, therefore, cognitive function. In the present study, it was theorized that arterial stiffness created by an acute bout of resistance exercise would have the same effect on cognition as advancing age, with significant reductions in cognitive function. This hypothesis was based on a number of previous studies, which found that an acute bout of resistance exercise leads to an increase in arterial stiffness (17, 24, 25, 48, 49, 66, 88). Unfortunately, the results of the present study were not as expected, as cognitive function was largely unaffected, and in some cases even improved slightly. This finding would suggest that the type of arterial stiffness induced with acute resistance exercise might not be physiologically identical to arterial stiffness brought about by old age.

Limitations:

The authors recognize that there are limitations to the present study. This study used young, healthy college-aged adults, free from any chronic disease. Therefore, the results and conclusions of the present study may not be applicable to older adults or those with chronic disease. In addition, the small sample size of this study, although meeting the burden of statistical significance, may warrant further investigation in the above discussed relationships. Previous studies of arterial function following resistance exercise have traditionally used carotid-femoral pulse wave velocity, the gold standard for this measure (4, 14, 24-26, 49, 66, 88). Due to

the variability in the time needed to take cfPWV, the present study used the Mobil-O-Graph, which has been previously validated against both cfPWV and an invasive measure of central aortic stiffness (62, 86). The final limitation was that the resistance exercise program used in the present study does not follow American College of Sports Medicine guidelines for general health promotion and disease prevention. While this is true, and it would not recommended to perform this program for use outside of a research setting, this program was utilized as it has been previously used to elicit an increase in central arterial stiffness (4, 41, 42).

Strengths:

The strengths of this study are also very important to consider. The cognitive testing protocol used during this study was extensive and provided insight to a number of different domains. In addition, gender was equally balanced among study participants, indicating that this effect applies to both males and females. Finally, the study group was very diverse, with a number of different ethnicities represented. This gives added credibility to the findings of the study, as they are applicable to a large number of people. Many other studies focus on one gender and/or ethnicity, meaning that while their results may be significant in a specific population, they have no broad implications. Given the diversity of the participants in the present study, it can be concluded that the aforementioned results hold true to nearly everyone. In addition, the uniform and high education level of all participants ensured that any result observed was not a result of preexisting variation in cognitive function.

Future Direction:

Future studies should investigate the mechanistic differences in arterial stiffness between younger and older subjects. There is clearly a disparity between the arterial stiffness induced with resistance exercise and the pathological arterial stiffness as a result of aging. These mechanisms should be further investigated as they may provide pertinent information for the treatment and prevention of cardiovascular disease. In addition, variations in intensity of acute resistance exercise should be further investigated to determine whether the inverted U-shaped curve holds true, or if an alternate pattern exists for the relationship between resistance exercise and cognitive function.

Implications:

The implications of this study lie in the use of resistance exercise as a means of physical fitness. It is currently recommended by the American College of Sports Medicine as part of a balanced exercise program for both healthy individuals and those with hypertension (19, 56). Therefore, if this study had found that an acute bout of resistance was detrimental to cognitive function, further investigation would be warranted.

Conclusion:

In conclusion, the present study found that an acute bout of resistance exercise did not have the anticipated effect on cognitive function. Increased arterial stiffness as a result of aging is a major risk factor for cognitive impairment. Previous

work on the hemodynamic response to acute resistance exercise showed that a single bout causes increases in central arterial stiffness. It was believed that this increase in stiffness mirrored that of the aging population, leading to the theory that cognitive function would decline as a result. The results of the present study suggest that in a young, healthy population free from other comorbidities, an acute bout of resistance exercise has no detrimental effects on cognitive function, and can even lead to improvements in certain areas.

Appendix:

Figure 11: Timeline for 2nd and 3rd Visits.

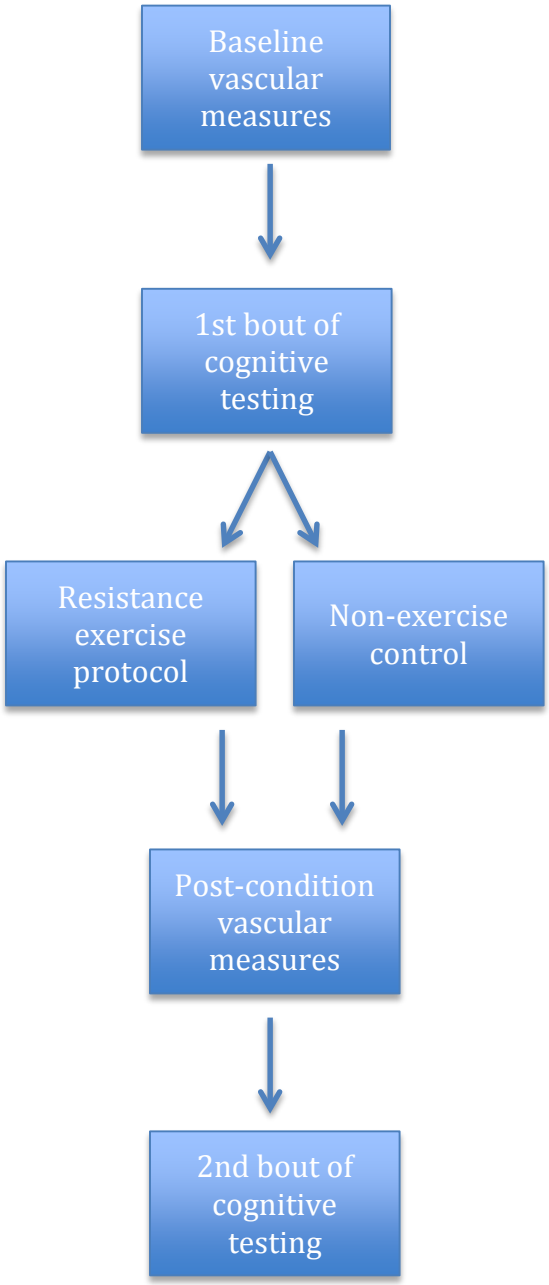

Table 3: Participant Characteristics

Variable	**n=20**
Age (years)	20.8 ± 1.1
Height (cm)	171.0 ± 8.9
Weight (kg)	72.7 ± 14.9
BMI (kg/m^2)	24.7 ± 3.4
MOCA	27.9 ± 1.3
Body Fat (%)	20.7 ± 8.7
5-RM Bench Press (lbs.)	120.3 ± 68.3
10-RM Biceps Curl (lbs.)	46.5 ± 19.3
Sleep (hours)	7.1 ± 1.0
Previous Resistance Exercise Experience	13
Concussion History	2
ADD/ADHD Diagnosis	3
IPAQ (MET-minutes/week)	3336.2 ± 1446.0
Average Sitting Time (hours/day)	9.5 ± 2.2

BMI= Body Mass Index
RM= Repetition Maximum

Table 4: Hemodynamic Data Across Condition and Time (Mean ± SD)

	Non-exercise control		Resistance Exercise		p		
Variable	**Pre**	**Post**	**Pre**	**Post**	**Condition**	**Time**	**Interaction**
Systolic Blood Pressure (mmHg)	118 ± 7	123 ± 15	118 ± 9	127 ± 17	0.310	0.100	0.980
Mean Arterial Pressure (mmHg)	93 ± 6	94 ± 8	93 ± 8	94 ± 11	0.895	0.218	0.877
Diastolic Blood Pressure (mmHg)	71 ± 6	71 ± 5	71 ± 9	66 ± 8	0.026	0.003	0.056
Peripheral Pulse Pressure (mmHg)	46 ± 6	52 ± 13	47 ± 9	61 ± 14*#	0.029	0.001	0.015
Heart Rate (bpm)	64 ± 12	61 ± 12	64 ± 12	75 ± 14*#	0.018	0.025	>0.001
Central Systolic Blood Pressure (mmHg)	111 ± 9	113 ± 15	108 ± 10	122 ± 18*#	0.254	0.003	0.006
Central Diastolic Blood Pressure (mmHg)	72 ± 6	72 ± 6	72 ± 9	68 ± 8	0.055	0.012	0.057
Central Pulse Pressure (mmHg)	37 ± 8	41 ± 13	35 ± 8	53 ± 16*#	0.038	>0.001	0.001
Augmentation Index @75bpm	9 ± 9	10 ± 16	11 ± 10	19 ± 17	0.123	0.143	0.208
Cardiac Output (mL/min)	5.5 ± 0.8	5.0 ± 0.7	5.4 ± 0.8	5.3 ± 1.4	0.666	0.036	0.237
Augmentation Pressure (mmHg)	5 ± 3	8 ± 8	6 ± 5	11 ± 12	0.320	0.500	0.412
Augmentation Index (%)	15 ± 8	18 ± 15	17 ± 13	19 ± 17	0.578	0.263	0.915
Reflection Magnitude (%)	61 ± 8	62 ± 11	60 ± 6	68 ± 7*#	0.332	0.014	0.015
Total Vascular Resistance	1.04 ± 0.18	1.15 ± 0.22	1.06 ± 0.19	1.11 ± 0.29	0.811	0.016	0.522
Cardiac Index	3.0 ± 0.4	2.7 ± 0.4	2.9 ± 0.5	2.9 ± 0.7	0.566	0.012	0.301
P1 (mmHg)	105 ± 10	105 ± 12	101 ± 12	110 ± 20	0.679	0.036	0.100
P2 (mmHg)	111 ± 9	113 ± 15	108 ± 10	122 ± 18*#	0.254	0.003	0.006
Pb (mmHg)	15.5 ± 3.9	17.0 ± 6.5	14.4 ± 4.0	22.8 ± 7.8*#	0.056	>0.001	0.001
Pf (mmHg)	24.9 ± 5.2	26.7 ± 7.5	24.0 ± 6.0	32.7 ± 8.9*#	0.037	0.001	0.002
Pulse Wave Velocity (m/s)	5.0 ± 0.3	5.1 ± 0.5	4.9 ± 0.4	5.4 ± 0.6*#	0.159	0.009	0.006
P1-cDBP	32 ± 9	32 ± 11	29 ± 10	42 ± 17*#	0.161	0.002	0.022
Stroke Volume (mL)	88.4 ± 17.5	85.1 ± 18.0	85.6 ± 13.2	72.7 ± 18.6	0.054	0.020	0.122

* Significantly different from Pre within same condition $p<0.05$

Significantly different from other condition, same time point $p<0.05$

Table 5: Cognitive Performance on Paper Tests by Domain Across Condition and Time (Mean ± SD)

			Non-exercise control		Resistance Exercise		p		
Domain	**Task**	**Variable**	**Pre**	**Post**	**Pre**	**Post**	**Condition**	**Time**	**Interaction**
Executive Function	Trail Making	Trails A (seconds)	16 ± 5	15 ± 3	15 ± 4	14 ± 3	0.194	0.014	0.993
		Trails B (seconds)	38 ± 18	30 ± 9	32 ± 10	28 ± 9	0.142	0.003	0.147
Verbal Fluency	Word Naming	Words Named in 60 Seconds	15 ± 5	17 ± 4	16 ± 4	18 ± 5	0.534	>.001	0.829
Memory	Digit Substitution	Total Completed in 90 Seconds	65 ± 9	56 ± 9	69 ± 10	57 ± 13	0.098	>.001	0.354

Table 6: Cognitive Performance and Reaction Times by Domain Across Condition and Time (Mean ± SD)

			Non-exercise control		Resistance Exercise		p		
Domain	**Task**	**Variable**	**Pre**	**Post**	**Pre**	**Post**	**Condition**	**Time**	**Interaction**
Attention	Flanker	Congruent-Number Correct	63 ± 1	62 ± 2	63 ± 1	63 ± 1	0.524	0.476	0.924
		Incongruent-Number Correct	60 ± 3	60 ± 3	61 ± 2	60 ± 3	0.670	0.394	0.566
		Percent Congruent Correct (%)	98.5 ± 2.8	98.1 ± 3.3	98.9 ± 1.7	98.5 ± 2.7	0.524	0.476	0.924
		Percent Incongruent Correct (%)	94.9 ± 6.2	94.5 ± 5.4	95.7 ± 3.9	94.6 ± 6.1	0.670	0.394	0.566
		Incongruent Average RT-Incorrect (ms)	542 ± 282	595 ± 419	710 ± 483	544 ± 297	0.460	0.647	0.364
		Incongruent Average RT-Correct (ms)	527 ± 50	522 ± 44	538 ± 48	502 ± 39*#	0.533	0.004	0.022
		Congruent Average RT-Incorrect (ms)	557 ± 38	1241 ± 140	1082 ± 591	957 ± 340	0.730	0.118	0.190
		Congruent Average RT-Correct (ms)	444 ± 58	442 ± 49	452 ± 41	419 ± 37*#	0.364	0.019	0.020
Executive Function	N-back	Total Commission Error	2 ± 3	3 ± 3	3 ± 2	2 ± 2	0.530	0.350	0.116
		Percent Commission Error (%)	1.7 ± 2.1	1.9 ± 1.6	1.8 ± 1.6	1.2 ± 1.4	0.530	0.350	0.116
		Correct Matches	16 ± 2	16 ± 3	16 ± 2	16 ± 2	0.675	0.792	0.623
		Percent Correct Hits (%)	81.7 ± 12.8	81.2 ± 17.3	81.7 ± 12.9	83.2 ± 12.2	0.675	0.792	0.623
		Average RT-Hit (ms)	536 ± 71	534 ± 76	504 ± 97	491 ± 61	0.014	0.576	0.573
Memory	Word Recognition	Total Hits	20 ± 5	21 ± 5	20 ± 4	20 ± 4	0.565	0.162	0.481
		Total False Alarms	11 ± 4	13 ± 4	10 ± 4	11 ± 5	0.134	0.109	0.228
		Percent Correct (%)	55.5 ± 13.9	60.6 ± 15.6	55.9 ± 13.1	57.2 ± 13.7	0.565	0.162	0.481
		Percent False Alarm (%)	31.2 ± 13.3	36.9 ± 13.4	30.4 ± 13.5	31.2 ± 15.0	0.134	0.109	0.228
		Average RT-Hit (ms)	889 ± 176	849 ± 149	883 ± 147	815 ± 155	0.295	0.010	0.445
		Average RT-False Alarm (ms)	957 ± 213	892 ± 195	938 ± 157	856 ± 206	0.302	0.007	0.790

RT= Reaction Time

* Significantly different from Pre within same condition $p<0.05$

Significantly different from other condition, same time point $p<0.05$

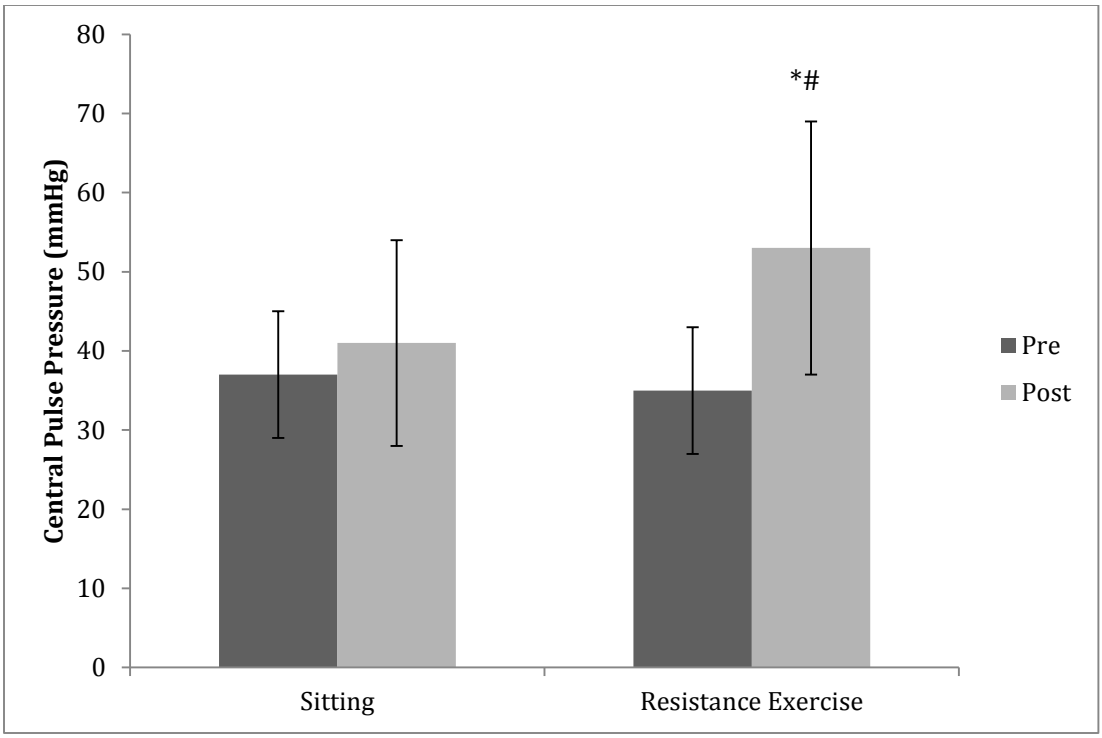

Figure 12: Differences in Central Pulse Pressure Across Condition and Time.
* Significantly different from Pre within same condition p<0.05
# Significantly different from other condition, same time point p<0.05

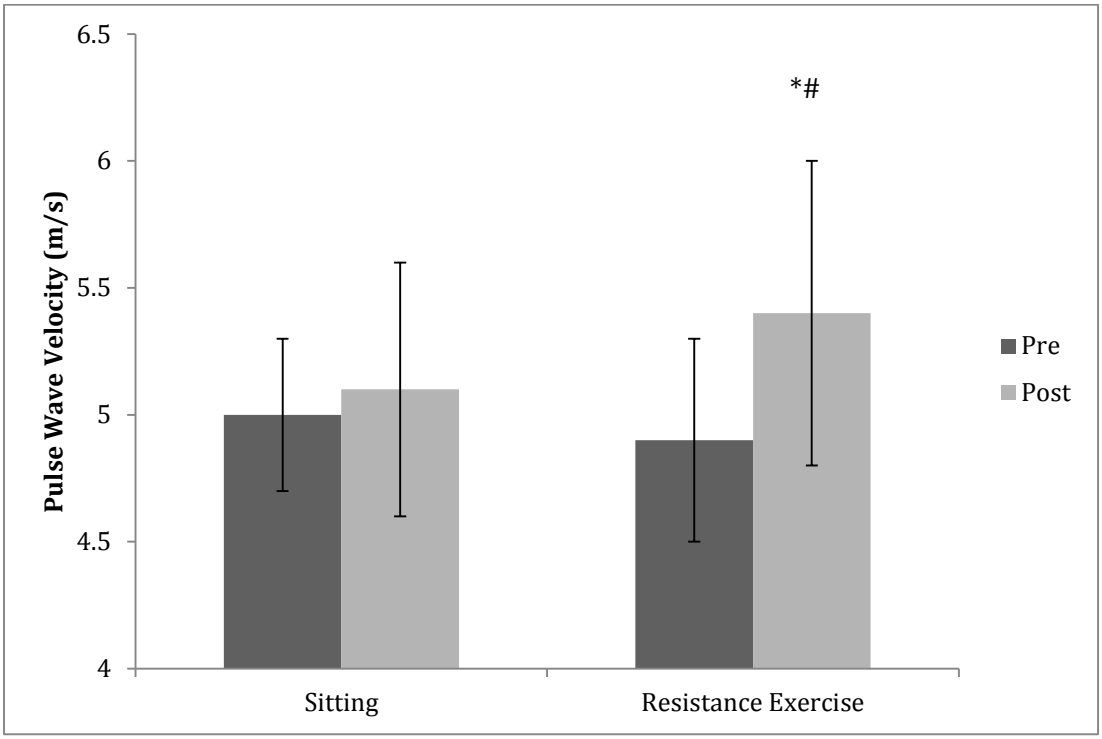

Figure 13: Differences in Pulse Wave Velocity Across Condition and Time.
* Significantly different from Pre within same condition p<0.05
# Significantly different from other condition, same time point p<0.05

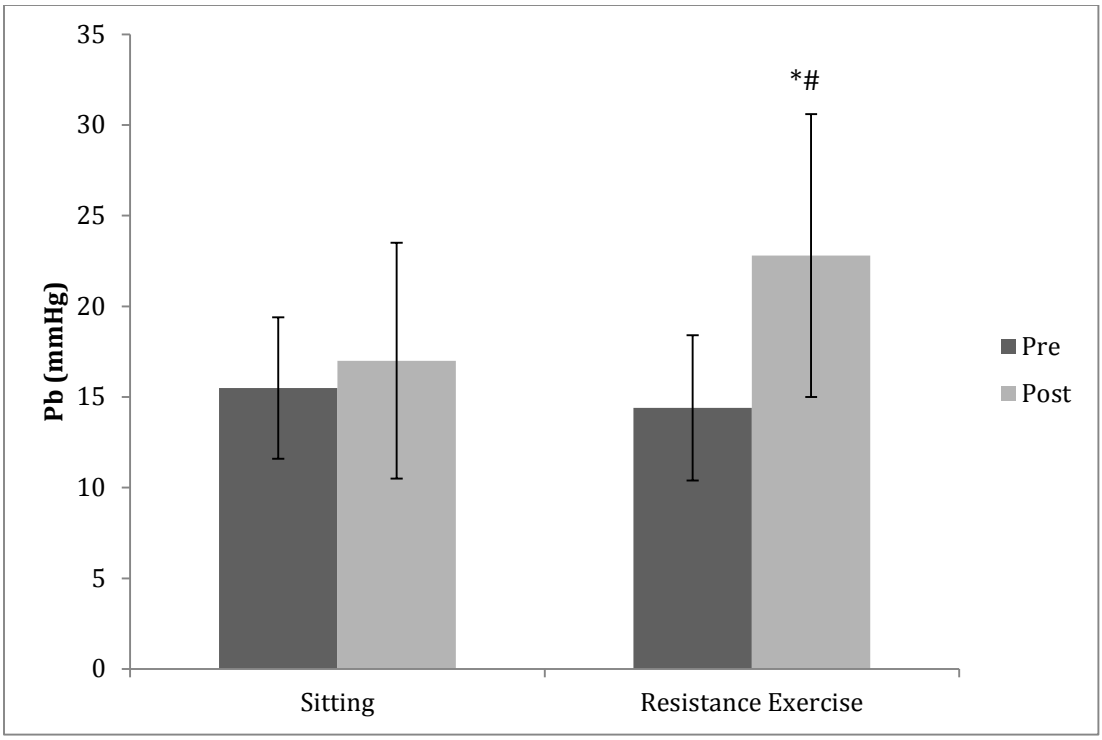

Figure 14: Differences in Pb Across Condition and Time.
* Significantly different from Pre within same condition p<0.05
# Significantly different from other condition, same time point p<0.05

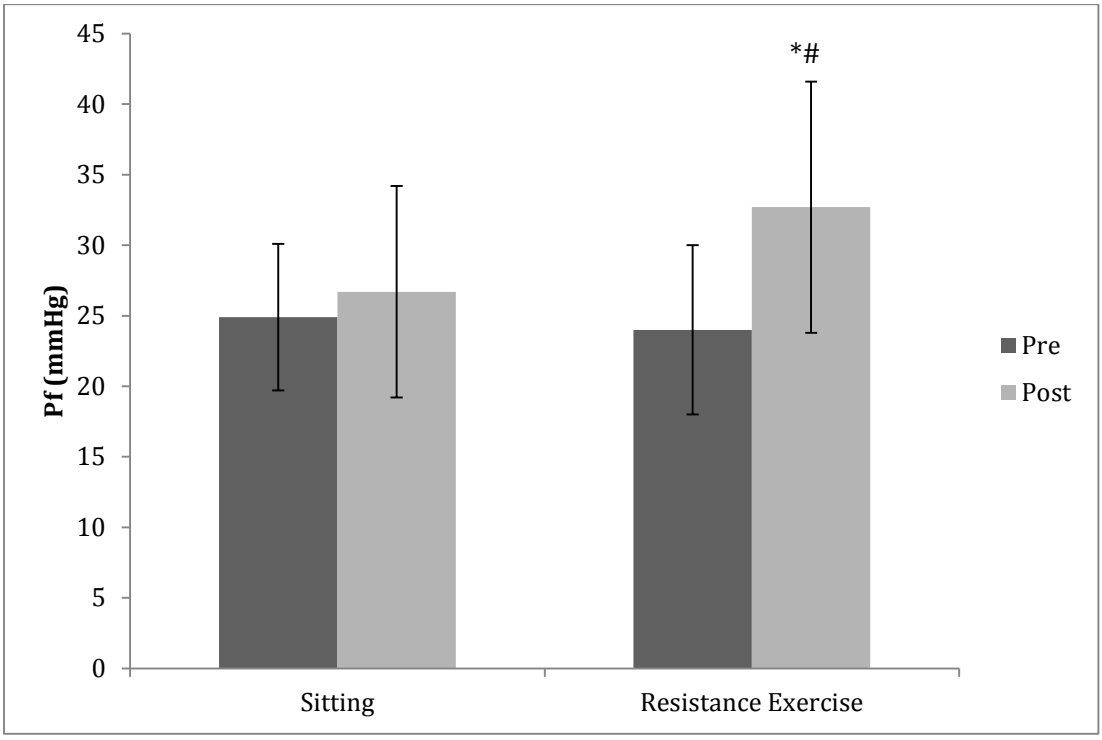

Figure 15: Differences in Pf Across Condition and Time.
* Significantly different from Pre within same condition p<0.05
# Significantly different from other condition, same time point p<0.05

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