The Effect of Resistance Training on Arterial Stiffness and Central Hemodynamics

by

Nathan Weeldreyer

A Thesis Presented in Partial Fulfillment
of the Requirements for the Degree
Master of Science

Approved April 2020 by the
Graduate Supervisory Committee:

Siddhartha Angadi, Chair
Glenn Gaesser
Chong Lee

ARIZONA STATE UNIVERSITY

May 2020

ABSTRACT

Cardiovascular disease has long been one of the leading causes of morbidity in the world and places a large burden on the health care system. Exercise has been shown to reduce the risk of developing cardiovascular disease and the risk factors associated with it. Much of the focus of research has been on aerobic exercise modalities and their effect on these risk factors, and less is known in regard to the effect of resistance training. One novel risk factor for cardiovascular disease is arterial stiffness, specifically aortic stiffness. Aortic stiffness can be measured by carotid-femoral pulse wave velocity (PWV) and central pressure characteristics such as central blood pressures and augmentation index. The objective of this study was to assess the effect that two different 12-week long resistance training interventions would have on these measurements in sedentary, overweight and obese men and women (BMI ≥ 25 kg/m2). Twenty-one subjects completed the study and were randomized into one of the following groups: control, a low repetition/high load (LRHL) group which performed 3 sets of 5 repetitions for all exercises, and a high repetition/low load (HRLL) group which performed 3 sets of 15 repetitions for all exercises. Those in the resistance training groups performed full-body exercise routines on 3 nonconsecutive days of the week. Changes in arterial stiffness, central blood pressures, and brachial blood pressures were measured before and after the 12-week intervention period. PWV showed significant group by time interaction (p= 0.024) but upon post hoc testing no significant differences were observed due to the control group confounding (control: 7.6 ± 0.8 vs. 7.1 ± 0.8, LRHL: 6.7 ± 0.5 vs. 6.9 ± 0.5, HRLL: 7.03 ± 0.67 vs. 6.59). No other significant interactions or differences were observed for any of the variables tested. Based on the results of this study a 12-week long

resistance intervention training, neither high nor moderate-intensity resistance training, resulted in improvements in indices of vascular stiffness or central and peripheral blood pressures.

ACKNOWLEDGMENTS

I would like to thank the participants that took part in this study for the time that they gave and effort that they put forth throughout the study. I would also like to thank my fellow graduate students, Anthony Sablan and Sofklis Sarellis for their assistance in the training sessions. Without them this study would not have been completed.

Theresa Jorgensen who is the lab manager in the exercise physiology laboratory has been an invaluable resource over the course of this study. She assisted with the laboratory testing as well as performed all of the echocardiograms. Anytime any issues arose in the lab she would go above and beyond to ensure things went smoothly. She also took the time to teach me the measurements and make sure I understood how they worked. She has been a key part of my education.

I would also like to extend my gratitude to Sid Angadi who has served as my chair and mentor throughout my time at ASU. He has consistently pushed me to be a better researcher and to always understand the physiology behind everything. Even with his busy schedule he always found time to assist me when I had questions or ran into problems.

Lastly, I would like to thank my family , friends, and girlfriend who have lent their unconditional support during my time at ASU. They have kept me sane and put up with me even when I was a pain. Thank you for all of your support.

TABLE OF CONTENTS

CHAPTER Page

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

Overview

Atherosclerotic cardiovascular disease is the leading cause of morbidity and mortality globally according to a 2019 joint statement by the American College of Cardiology (ACC) and the American Heart Association (AHA). Cardiovascular disease also places a large burden on the health care system as evidenced by the 200 billion dollars in health care costs each year in America alone (Arnett et al., 2019). Cardiovascular disease (CVD) is a group of diseases that affect the heart and blood vessels and are often characterized by the stiffening and narrowing of arteries due to plaque buildup (D'Agostino et al., 2008).

The traditional CVD risk factors include age, sex, family history, smoking, hypertension, dyslipidemia, obesity, and diabetes (D'Agostino et al., 2008). While these major risk factors are still used, there have been novel risk factors that have been proposed and have shown prognostic value beyond the current major risk factors. These measures are pulse wave velocity (PWV) and pulse wave analysis (PWA), which are used to indirectly measure arterial stiffness, most commonly central or aortic, stiffness (Ben-Shlomo et al., 2014; Shirwany & Zou, 2010).

Current literature has shown these two tests have predictive value above current risk factors. A study done by Willum-Hansen et al. found a hazard ratio of 1.61 for those with a 1 standard deviation increase in PWV that when corrected for traditional risk factors was still significant at a hazard ratio of 1.2 (Willum-Hansen et al., 2006). Similarly, a study by Nürnberger et al. assessed the association between augmentation

index, a measure obtained through PWA, and CVD risk. They used 3 separate risk score calculators and found the augmentation index rose significantly as the risk scores went up and there was significant correlation with all 3 risk scores used ($P< 0.0001$) (Nürnberger et al., 2002).

As the central arterial system stiffens and PWV and central pressures increase, people are at risk for developing many forms of CVD such as coronary artery disease, stroke, heart failure, and are at higher risk for cardiac events (Ben-Shlomo et al., 2014; Nürnberger et al., 2002; Roman et al., 2007; Shirwany & Zou, 2010; Willum-Hansen et al., 2006). Due to this increased risk of developing disease there has been emphasis placed on ways to reduce PWV and PWA. One area that has traditionally been used to help with CVD risk is exercise.

Current exercise guidelines recommend a mix of aerobic exercise and resistance training in order to reduce the risk of developing a multitude of chronic diseases (American College of Sports Medicine, Riebe, Ehrman, Ligouri, & Magal, 2018). However, when looking at exercise and its health benefits, the emphasis is placed on aerobic activity. For example, the 2019 guidelines by the ACC/AHA for the reduction of CVD dedicate only a small portion of the paper to discussing the benefits of resistance training which include increased insulin sensitivity, possible blood pressure lowering effects, and increased physical functioning (Arnett et al., 2019).

Current guidelines recommend low to moderate training intensities for resistance training, for example the ACSM guidelines recommend 8-12 reps at 60-80% of 1 repetition maximum (American College of Sports Medicine, Riebe, Ehrman, Ligouri, & Magal, 2018). This is due to the thought that high-intensity training may cause

deleterious effects on the cardiovascular system such as increased blood pressure, arterial stiffness, and left ventricular mass (Miyachi et al., 2004). However, a previous statement by the AHA noted that the effect of resistance training on central and peripheral arterial compliance is inconsistent and controversial (Willliams et al., 2007). For example, a meta-analysis by Ashor et al. in 2014 analyzed 17 RCTs and found there were no significant differences in PWV before and after training interventions (Ashor, Lara, Siervo, Celis-Morales, & Mathers, 2014). Just a year before, a meta-analysis by Miyachi examined 8 RCTs and concluded there was a significant increase in PWV after higher intensity resistance training, particularly in younger subjects (Miyachi, 2013).

Based on these papers and many others, it is clear that the effect of high-intensity resistance training on the vascular system is still not fully understood. According to Williams et al. adding in resistance training to exercise prescriptions can be an important aspect due to increasing variety to training days and its possible ability to maintaining adherence to exercise programs (Williams et al., 2007). When resistance training is performed in accordance with ACSM guidelines, there have been shown cardiometabolic benefits. However, based on current literature it is unclear what the effect of resistance training performed exclusively as high load lifting has on CVD risk. Therefore, the purpose of this study was to investigate the chronic effect that high-intensity and moderate-intensity resistance training programs have on the cardiovascular system.

Purpose

The purpose of this study was to investigate the effects that high load and low load resistance training have on arterial stiffness and central hemodynamics. This served as a follow up randomized control trial to previous studies that have looked at the

relationship between resistance training and arterial stiffness and was performed to better understand the effect that high load training has on arterial stiffness.

Aim and Hypotheses

Primary Aim

The primary aim of this study was to determine the impact that two different 12-week resistance training interventions have on PWV compared to a non-exercising control in overweight and obese sedentary individuals.

Primary Hypothesis: It was hypothesized that there would be no change in PWV in either intervention group as compared to the control group.

Secondary Aim

The secondary aim of this study was to examine the effects that two different 12-week resistance training interventions have on PWA measures compared to a non-exercising control. These measures include Aix, Aix75, AP, and central systolic and diastolic pressures.

Secondary Hypothesis: It was hypothesized that central blood pressures would be significantly decreased in both of the intervention groups when compared to the control group. It was also hypothesized that augmentation indexes would be significantly reduced.

Tertiary Aim

The tertiary aim for this study was to perform an exploratory analysis of the effect that two different 12-week resistance training interventions have on minor functional changes of the left ventricle as measured by global longitudinal strain (GLS). The relationship between changes in arterial stiffness and GLS were also assessed.

CHAPTER 2

REVIEW OF LITERATURE

Background Information

According to a 2019 guideline for the prevention of cardiovascular disease by the American College of Cardiology (ACC) and the American Heart Association (AHA) atherosclerotic cardiovascular disease is the leading cause of morbidity and mortality globally. In America cardiovascular disease accounts for over 200 billion in health care costs each year (Arnett et al., 2019). Cardiovascular disease (CVD) is a group of diseases that affect the heart and/or the blood vessels throughout the body. Common diseases that fall under this are coronary artery disease, heart failure, peripheral artery disease, and cerebrovascular disease (D'Agostino et al., 2008). These diseases are characterized by the stiffening and narrowing of arteries due to plaque buildup over time. CVD and the accumulation of plaque in the arterial system have a set of major risk factors.

The major risk factors usually associated with CVD are age, sex, family history, smoking history, hypertension, dyslipidemia, and diabetes (D'Agostino et al., 2008). However, in recent years there have been novel risk factors proposed which may lead to an increased risk of developing CVD. One of these risk factors is arterial stiffness, specifically aortic stiffness (Ben-Shlomo et al., 2014; Shirwany & Zou, 2010). Two tests that can be done in order to indirectly assess aortic stiffness are pulse wave velocity and pulse wave analysis.

A recent meta-analysis by Ben-Shlomo et al. examined the event prediction capabilities of the PWV assessment, specifically the carotid-femoral pulse wave velocity (cfPWV) the current gold standard test for indirect arterial stiffness measurement. This

meta-analysis looked at data from over 17,500 subjects and the outcome measures included all-cause mortality, cardiovascular mortality, CHD events, and stroke. They found that each of the hazard ratios for these events significantly increased in those who had a 1 SD change in Log_e in cfPWV with CVD hazard ratio being 1.45. When they adjusted for the traditional risk factors associated with CVD, they still found increased hazard ratios (1.3 for CVD). For a healthy 60-year old male they found an increase of 1 m/s in cfPWV resulted in a 7% increased likelihood for a cardiovascular event. They concluded that even after adjusting for traditional CVD risk factors, cfPWV was still able to predict future CVD events (Ben-Shlomo et al., 2014).

A similar study by Willum Hansen et al. in 2006 looked at 1,678 Danish citizens aged 40-70 years old. The researchers took measurements of in-office pulse pressure, 24-hour ambulatory pulse pressure, and a pulse wave velocity measurement. Then they followed up with the subjects for a median of 9.4 years. They examined the hazard ratios associated with a 1 SD increase in all 3 measurements (SD= 13mmHg for pulse pressure, 9mmHg for ambulatory pulse pressure, and 3.4m/s PWV). For cardiovascular mortality they found hazard ratios of 1.85, 1.70, and 1.61 for pulse pressure, ambulatory pulse pressure, and PWV respectively. However, when these findings were adjusted for age, sex, body mass index (BMI), mean arterial pressure (MAP), smoking history, and alcohol intake, the only measure that still had a significantly greater hazard ratio was PWV, being 1.20 (Willum Hansen et al., 2006).

While PWV has shown prognostic value above the current primary risk factors for cardiovascular disease, pulse wave analysis has also shown promising results in better predicting incidences of various cardiac events. Briefly, pulse wave analysis (PWA) is a

non-invasive measurement taken through either applanation tonometry or through the volumetric displacement of a standard blood pressure cuff (Butlin & Qasem, 2016). This test provides us with measures such as central blood pressure, augmentation pressure (AP), augmentation index (Aix), and Aix corrected for a heart rate of 75 bpm (Aix75) and can be used to assess arterial stiffness, all of which will be discussed in detail in the next section.

A study by Nürnberger et al. in 2002 assessed the association between the augmentation index and cardiovascular disease risk. This study looked at 216 individuals, both healthy and those diagnosed with some form of cardiovascular disease. They performed a pulse wave analysis assessment using applanation tonometry and used 3 separate risk predictors on each participant to assess the relationship between Aix and CVD risk. The 3 risk scores used in this study were: the European Society of Cardiology risk score (ESC risk score), which estimates the risk of developing coronary heart disease in the next ten years, the SMART risk score which predicts the risk of cardiovascular events occurring in the next ten years, and finally the EPOZ risk score, which predicts the probability of dying in the next 11.5 years.

They found that the augmentation index rose significantly as risk scores went up and was significantly correlated with all 3 of the risk scores used in the study ($P < 0.0001$). The study also noted this relationship was present in both the healthy group and those with CVD (Nürnberger et al., 2002). While this was a cross-sectional study and causation cannot be determined, there is a clear relationship between augmentation index and cardiovascular disease risk.

A study conducted by Weber et al. in 2004 looked at the risk for coronary artery disease (CAD) based on arterial pulse wave analysis. For this study they performed PWA on male subjects who were going in for coronary angiography. Those who were found to have at least one 50% or greater blockage in one or more coronary vessels or those who already had a previous stent placed were classified as having significant CAD. They found that the different PWA measurements were significantly associated with CAD (Aix: $p= 0.007$, AP: $p= 0.004$, Ax75; $p= 0.01$). They also found there were significant correlations between AP and Aix75 and the severity of CAD based on the angio-scores. Even after adjusting for age, height, cholesterol, and medication usage there was still a significant association between Aix and CAD. When looking at age differences they found that those who were under 60 years old had stronger correlations (Weber et al., 2004).

While brachial blood pressures are able to give us important information and can be used as a traditional risk factor, measures of central pressures and pulse wave characteristics give us greater insight. As the pulse wave travels through the arterial tree the pressure is amplified, and therefore the pressures centrally can differ greatly from those found at the brachial artery. The central pressure gives us an accurate look at the loads that are placed on the left ventricle (Laurent et al., 2006). The combination of PWV and PWA gives us a better picture of the characteristics of the aorta and the conditions the heart and other target organs are placed under.

Global longitudinal strain has also been shown to have prognostic value. When trying to assess the systolic function of the heart, ejection fraction (EF) has traditionally been the measure that has been used, particularly left ventricular ejection fraction

(LVEF). However more recently, GLS has been shown to have a better predictive value than EF. A review by Potter and Marwick discusses how an EF can be normal even in the presence of systolic dysfunction, this being due to left ventricular hypertrophy and having a small stroke volume. They also discuss that while EF has prognostic value and is inversely correlated with all-cause mortality, this is only true when LVEF is below 40-45%, above which it is unrelated to mortality (Potter and Marwick, 2018).

Additionally, a meta-analysis by Stanton et al. examined over 5,700 subjects found GLS is a strong predictor of all-cause mortality, cardiac death, heart failure hospitalization, as well as malignant arrhythmias (Stanton et al., 2009). While GLS is currently most used for the assessment of left ventricular dysfunction in those undergoing chemotherapy treatments for cancer, it has also shown promise in other clinical populations. The first of these is hypertensive patients where reductions in strain can be seen independent of LV hypertrophy and diastolic dysfunction (Szelenyi et al., 2015). In diabetic patients, systolic dysfunction has been seen in more than half of asymptomatic subjects (Potter and Marwick, 2018). A study by Ernade et al. assessed diabetic patients and found that changes in systolic function were present in nearly a third of patients who still had normal diastolic characteristics. This led them to the conclusion that changes in strain may be an early clinical marker for diabetic cardiomyopathy (Ernande et al., 2011).

When looking at the current literature, there is a strong case for the use of novel techniques for the detection of early signs of cardiovascular disease. GLS based changes in myocardial function can be seen even before changes in hypertrophy or diastolic dysfunction in hypertensive and diabetic patients respectively. This can result in early detection of cardiac function and possible retarding of the progression of cardiovascular

disease. Similarly, PWA and PWV measurements have shown clear evidence that the use of arterial stiffness and central blood pressure measures have predictive value above current risk factors. Thus, these tests should be used to assess the general population to increase detection of potential disease states.

Pulse Wave Analysis

As early as the late 19th century we have been able to measure pulse pressures and even analyze the pulse wave of the radial artery. This was due to sphygmography, a device that could be fitted around the wrist and would draw out the resulting waveform (Hirata, Kawakmai, & O'Rourke, 2006; Noon, 2009). However, this was replaced by the modern-day cuff sphygmomanometer and focus was shifted to brachial blood pressure measures. Recently the concepts of arterial stiffness and central hemodynamics and their role in cardiovascular disease have been looked at with more importance due the idea that systolic, diastolic, and pulse pressures are related to the physical properties of the arteries (Noon, 2009). While PWV is considered the "gold standard" measure of arterial stiffness, PWA gives us another way of measuring arterial function and allows us to analyze other parameters than PWV alone (Doupis, Papanas, Cohen, McFarlan, & Hortan, 2016).

When PWA is performed the parameters given are: Central blood pressures, brachial blood pressures, augmentation pressure (AP), augmentation index (Aix), and augmentation index corrected for a heart rate of 75 beats per minute (Aix75). The test can be performed using multiple methods including applanation tonometry of the radial or carotid arteries or using a specialized cuff equipped with a high-fidelity micromanometer at the brachial artery. The waveforms measured at these peripheral sites are analyzed

using a transfer function (discussed later) and central parameters are then given (Butlin & Qasem, 2017; Davies & Struthers, 2005).

When the heart beats, a pressure wave is created and travels forward through the arterial tree. It first encounters large elastic arteries such as the aorta, carotid, and iliac arteries. When the pressure waveform reaches areas of impedance, such as the more muscular peripheral arteries and bifurcations, a reflected wave is created. This causes the forward-moving wave to be amplified and continue to move forward, and the reflected pressure waveforms travel back toward the heart. In young and healthy individuals this reflected waveform arrives back to the heart in diastole or late systole. When it arrives at this point at the cardiac cycle it aids in coronary perfusion due to augmenting diastolic pressure. However, when the large elastic central arteries are stiff, the pressure waves travel faster. This results in the reflected wave arriving back at the heart sooner, during systole, and augments systolic pressure. When this happens the reflected pressure wave interacts with the forward-moving wave as it leaves the left ventricle. This causes increased pressures and appears as a shoulder in the pulse pressure waveform. When examining a central pulse pressure waveform, the first increase in pressure is from the forward moving wave. The first shoulder marks where the reflected wave arrives, and this augments the pressure measured. The difference in pressure from the first shoulder to the peak pressure measured is called the augmentation pressure (Shirwany & Zou, 2010).

Another measure analyzed during PWA is the augmentation index (Aix). This measure is used as an indirect estimate of arterial stiffness (Shirwany & Zou, 2010; Doupis, Papanas, Cohen, McFarlan, & Hortan, 2016). Instead of looking at the absolute increase in pulse pressure like the AP, the augmentation index is a measure of the

contribution of the reflected wave to the overall pulse pressure (Stoner et al., 2014). It is calculated by dividing the augmentation pressure by the pulse pressure and multiplying by 100. The augmentation index is also given corrected for a heart rate of 75 bpm. The Aix is affected by the heart rate that it corresponds with. Therefore, in a study that is taking multiple measurements and looking at many participants this measure is important. It allows the researcher to compare Aix of the same participant who may have a different HR between measurements and also between different groups of participants.

The final measurement given by PWA is central blood pressure. As stated above, due to the physical properties of the arterial system, the pressure is amplified as it travels through the arterial tree. This is due to the shift from large elastic arteries found centrally to the more muscular arteries controlled by a vasomotor tone and is known as the "amplification phenomenon" (Laurent et al., 2006). Due to this phenomenon, the pressure found centrally can differ significantly from that measured at peripheral sites such as the brachial artery. For example, Roman et al. found a 10mmHg difference measured between brachial and central systolic pressures, 130mmHg brachial SBP compared to 120mmHg central SBP ($P< 0.001$) (Roman et al., 2007). While blood pressure found at the periphery can give a general idea of blood pressure, it does not accurately reflect the conditions in the entire arterial system. In the context of CVD, it also does not give an accurate depiction of what the main target areas of this disease are put under. The central pressure is what the left ventricle, coronary arteries, cerebral system, and the renal system will be placed under, not the peripheral pressures. Therefore, central pressure provides better insight into the loading that these target organs experience (Roman et al., 2007).

While arterial stiffness can be measured directly using an ultrasound/catheter tip manometer system, this involves an invasive procedure and therefore does not make sense to use in a clinical setting (O'Rourke, Staessen, Vlachopoulos, Duprez, & Plante, 2002). However, commercial systems such as the SphygmoCor system (AtCor Medical, Sydney, Australia) allow for the noninvasive measurement of arterial stiffness through the use of a transfer function. In the 1970s O'Rourke and Lasance used a transfer function to assess the relationship between aortic and brachial artery pressures in those with valve disease and atrial fibrillation undergoing cardiac catheterization. They found the transfer functions were similar among all patients looked at, although patient characteristics varied (Hirata, Kawakmai, & O'Rourke, 2006).

In 1993, Karamanoglu again found similar results looking at patients with coronary artery disease. After analyzing published data, they found that an average transfer function could be used to recreate accurate pressure waveforms in the aorta from waveforms analyzed in the upper arm (Karamanoglu, O'rourke, Avolio, & Kelly, 1993; Hirata, Kawakmai, & O'Rourke, 2006). This average transfer function was coined the Generalized Transfer Function and is the basis for noninvasive central pulse wave analysis used in commercial devices.

Pulse Wave Velocity

While PWA measurements such as the Aix can be used as an indirect measure of arterial stiffness, PWV is a more direct measure of stiffness (Zhong et al., 2018). PWV is a measure of the speed at which the pressure wave travels through the arterial system. This is performed by measuring the pulse at two sites on the body and dividing the distance by the travel time of the pulse. While this measurement can be taken at multiple

sites, for central, or aortic PWV, the pulse is measured at the carotid and femoral arteries (cfPWV) (Hirata, Kawakmai, & O'Rourke, 2006). This measure can be found in one of two ways. The first is using applanation tonometry at both sites and a simultaneous ECG used to time for the R-wave. The second method uses applanation tonometry at the carotid site and a cuff-based method similar to the one used in PWA at the femoral site (Butlin & Qasem, 2017).

Similar to arteries in the rest of the body, the aorta is susceptible to a variety of conditions which can cause it to stiffen and become less compliant. Central arteries, such as the aorta, are large and elastic. Due to this, when the heart beats, this elasticity causes the forward pulse wave to have a relatively low velocity. This slow velocity allows for the reflected pressure wave to return to the heart late in late systole or early diastole which provides favorable diastolic pressure and allows for good circulation to the coronary arteries (Shirwany & Zou, 2010).

However, as we age the arterial tree becomes less compliant (stiffer). This is due to changes in the arteries such as intimal thickening, plaque formation, increased calcium deposits, greater collagen levels, and endothelial dysfunction. All of these lead to changes in the physical makeup of the arteries and result in stiffer arteries (Zhong et al., 2018). This stiffening results in a less compliant artery which does not provide a "cushioning" effect that would decrease the speed at which the blood travels through the vascular system. While stiffening occurs due to aging, diseases such as hypertension and diabetes can cause premature stiffening due to changes in the mechanical properties of the vasculature. As noted above there are multiple reasons for decreased compliance in arteries. When the arteries are exposed to increased pressure over long periods of time

(hypertension) or with chronic inflammation (diabetes), there is an increased production of collagen and decreased production of elastin. Over time this mismatch in production results in structural changes and leads to stiffening of the arteries (Shirwany & Zou, 2010).

When the arteries stiffen and central blood pressures increases, the afterload that the heart has to overcome is increased. Overtime this leads to increased left ventricular hypertrophy, LV wall thickness, and LV mass index (Miyachi et al., 2004). Previous meta-analyses have examined the changes in LV geometry and functional changes. Zhang et al. found that there were no changes in LV ejection fraction after resistance training and combination training in those with CVD (Zhang et al., 2018). However, as mentioned previously, a 2018 review stated the global longitudinal strain is a more sensitive measure of cardiac function than ejection fraction (Potter & Marwick, 2018). Therefore, changes in global longitudinal strain will be assessed to measure changes in cardiac function.

Furthermore, if changes in arterial stiffness occur, there could be relationships present between changes in arterial stiffness and myocardial strain. As noted above, as stiffness increases, so does the work of the heart and in turn left ventricular hypertrophy increases. Based on this knowledge, it is hypothesized that as measures of arterial stiffness increase a resulting decrease in global longitudinal strain will occur and vice versa. Therefore, correlations between markers of arterial stiffness and strain will be run to test this hypothesis.

When the central arterial axis stiffens and pulse wave velocity increases, changes in the pulse wave can be seen. As discussed earlier, the changes that are seen include a

higher systolic pressure that is attributed to the augmentation of the pressure waveform from the reflected wave. Increased PWV and therefore increased central pressures have been associated with many diseases. These include coronary artery disease, atrial fibrillation, heart failure, stroke, and have shown an increased risk for CVD and increased cardiovascular events (Ben-Shlomo et al., 2014; Nürnberger et al., 2002; Roman et al., 2007; Shirwany & Zou, 2010; Willium-Hansen et al., 2006). Due to this increased risk profile associated with increased pulse wave velocity and increased central pressures, the emphasis has been placed on ways to reduce these measurements. One area that has been traditionally used to help with CVD risk is exercise.

Current Exercise Guidelines

The ACSM has exercise guidelines for the general public to reduce CVD risk. The guidelines for exercise are a total of 150 minutes of moderate to vigorous aerobic activity a week performed 3-5 days a week. They also include resistance training guidelines which are 2-3 days a week of 2-4 sets of 8-12 reps (60-80% 1RM) focusing on all the major muscle groups. These recommendations have shown many health benefits including lowering blood pressure, decreased CVD risk and event rate, improving lipid and c-reactive protein profiles, and improving insulin sensitivity (American College of Sports Medicine, Riebe, Ehrman, Ligouri, & Magal, 2018; Garber et al., 2011).

However, a majority of these health benefits can be said to be due to aerobic exercise compared to resistance training in the general population. In the 2019 guidelines for the prevention of cardiovascular disease by the ACC/AHA, the majority of exercise discussion is focused on the benefits of aerobic exercise on CVD risk reduction. Only a small portion of the paper is dedicated to resistance training and its benefits, which

include increased insulin sensitivity, increased physical functioning, possible blood pressure lowering effects, and possible CVD risk reduction (Arnett et al., 2019). While aerobic exercise has shown to have a beneficial effect on the cardiovascular system, less is known about the effect of resistance training on cardiovascular health.

Current guidelines put in place by many organizations such as the ACSM, ACC, AHA recommend resistance training prescriptions of 8-12 reps at 60-80% of 1 repetition maximum (1RM). These are relatively lower intensity prescriptions. This is due to the idea that higher intensity resistance training prescriptions can lead to increased arterial stiffness and increased blood pressures, something that should be avoided. However previous statements by the AHA have stated the effect of resistance training on central and peripheral compliance remain inconsistent and controversial. This same statement also notes that resistance training can be an important aspect to add to training programs, as it adds variety and potentially assists in maintaining adherence to exercise programs. (Williams et al., 2007). Therefore, it is important to understand exactly how resistance training affects the hemodynamic profile of those undergoing training. While lower intensity programs are generally accepted as having neutral or even beneficial effect on cardiovascular characteristics, current literature is inconsistent when looking at higher intensity programs.

Resistance Training and Arterial Stiffness

When looking at the effect of resistance training programs, especially high-intensity programs, there is still debate on the effect it has on the cardiovascular system. For example, a meta-analysis by Ashor et al. in 2014 found that resistance training alone had no significant effect on PWV (WMD= -0.04, p= 0.82). This meta-analysis examined

17 randomized control trials that had weightlifting only interventions. The examined interventions ranged from 8-16 weeks and typically were completed about 3 times per week. The intensity of the studies examined ranged from 40-100% of 1RM but most were around 80% of 1RM. When running a subgroup analysis, they also did not find any relationships based on exercise intervention characteristics (Ashor, Lara, Siervo, Celis-Morales, & Mathers, 2014).

Statistically there were no differences between pre and post measures of PWV in the meta-analysis, but even if the WMD of -0.04 m/s was significant, this does not relate to much clinical significance. The current guide for clinical significance for PWV is that for every 1.0 m/s increase there is a 12-15% increase in CVD risk and CVD mortality so a change that small would not mean much. This meta-analysis also looked at Aix and found there was a nonsignificant reduction in Aix (WMD= -1.69%, p= 0.17) (Ashor, Lara, Siervo, Celis-Morales, & Mathers, 2014). Based on this study it would seem that while there are no beneficial effects on the cardiovascular system, there were also no detrimental effects.

This study by Ashor et al. comes to the opposite conclusion as a study done by Miyachi just a year earlier. The meta-analysis performed by Miyachi in 2013 examined 8 randomized control trials that looked at resistance training and its effect on PWV as well as the carotid beta index. They found that overall resistance training had a negative effect on arterial stiffness. They further looked at the studies using subgroup analysis and found the studies that used high-intensity training (>70% 1RM) had significant increases in stiffness, but those using moderate intensity (40-70%) training did not. They also found that the 3 studies examining older subjects did not increase measures of stiffness, but the

5 that used younger subjects did result in increased stiffness. However, it should be noted that 4 out of the 5 studies using younger subjects used high-intensity protocols, and all 3 studies looking at older subjects used moderate-intensity protocols (Miyachi, 2013).

While he concludes that overall resistance training did have a negative effect on arterial stiffness, it appears that only studies using protocols above 70% of 1RM show this increased stiffness. The author does note however that since the increased stiffness is seen only in younger participants (these study's average ages ranged from 19.1-22 years old) who started with low baseline levels of stiffness it may not be clinically significant. The overall increase in PWV was 0.72 m/s, and while this is nearing the 1 m/s increase in PWV that is deemed clinically significant, those who are young may not see such large increases in CVD risk due to having low baselines (Miyachi, 2013). After looking at two meta-analyses published one year apart, focused solely on RCTs, there are already conflicting results.

A study by Au et al. found that resistance training protocols improved measures of arterial stiffness. This was a randomized control trial consisting of a 12-week intervention that investigated the effect of a high vs. low repetition protocol on pulse wave velocity. This study recruited 32 healthy men who had a history of strength training (at least 2 years training at least 2 times a week). Participants were randomized into either a control, low rep (3 sets of 8-12 reps), or a high rep (2 sets of 20-25 reps) group. After the 12-week intervention they found that both the high rep and low rep group had decreased their pulse wave velocities. The high rep group went from 6.4± 0.7 to 5.7± 0.6 m/s ($P < 0.05$) and the low rep group went from 6.2± 0.6 to 5.8± 0.8 m/s ($P < 0.05$) and no significant changes were seen in the control group (Au et al., 2017).

This study looked at those with a training history, which is unlike many studies that look at resistance training, which typically recruit those without significant training history. Due to this, it is interesting to see a significant decrease in pulse wave velocities, though this could be due to the training prescription. While the authors call one of their groups low rep, sets of 8-12 are more in line with the moderate-intensity training prescribed by the ACSM with their high rep group completing a very low-intensity routine (30-50%) (American College of Sports Medicine, Riebe, Ehrman, Ligouri, & Magal, 2018; Garber et al., 2011; Au et al.,2017). The control group in this study maintained their current level of activity throughout, which included their own lifting program they had been following up to that point. The study does not indicate the average training protocol undertaken by those in the control group, so it cannot be determined if there were large differences in the training interventions. Based on this study, it appears that reductions in markers of arterial stiffness can occur in those with a previous history of resistance training (Au et al., 2017).

The study by Morra et al. also examined those with a long history of resistance training. This was a cross-sectional epidemiological study that sought to assess the relationship between long term weightlifting on a multitude of cardiovascular outcomes. Morra et al. recruited 69 healthy men aged 20-50 years old that had a history of either endurance running or high-intensity weightlifting, and a control of healthy untrained participants. Those who were endurance runners had to have been training for either half or full marathon distances for greater than two years, train at least 4 times a week, and have a baseline VO_2max of at least 50 ml/kg/min. Those in the resistance training group had to have been training at least 2 years with 90% of their training performed at greater

than 80% of 1RM, 5 sessions minimum per week, and a BMI of at least 27 kg/m^2 (Morra et al., 2014).

The average training history for both the aerobic and resistance training athletes was similar, 9.4 years and 9.1 years respectively. They found that PWV was significantly lower in both training groups when compared to the untrained, age-matched control group. The average PWV for those in the resistance training group was 7.5± 0.13 m/s and was 7.2± 0.14 m/s in the endurance runners compared to 8.2± 0.16 m/s in the control group ($p< 0.05$ for both groups). They also found that there were no significant differences in central pressure between any of the three groups. While this was not an RCT, and therefore no causation can be determined, this study showed that long term high intensity lifters have similar PWV and central pressures to those who are aerobically trained (Morra et al., 2014).

While the study by Mora et al. seems to show that long term high intensity resistance training does not have any negative effect on arterial stiffness, a review by Li et al. that looked at the effect of different exercise modalities on arterial stiffness in both normotensive and hypertensive adults concluded otherwise. This review analyzed 17 RCT, 11 of which involved resistance training alone. Training duration ranged from 8-16 weeks, and intervention intensities ranged from 20-100% of 1RM. Based on the studies that were analyzed they come to the conclusion that moderate to light resistance training does not have any negative effect on measures of arterial stiffness, but those who implemented protocols using intensities above 80% of 1RM resulted in increased measures of arterial stiffness (Li et al., 2015). While this is not a meta-analysis, it is a review of only RCTs and provides thorough review of current literature. One thing to

note with this study as well as many of those looking at resistance training, is that the majority of the participants are male. Few studies have examined the effect that weight training has on just women.

However, Cortez-Cooper et al. conducted a study in 2005 that looked exclusively at healthy young women. This study had a unique resistance training protocol when compared to most studies. Participants were randomized into either an 11-week control or resistance training period. The training was performed in a progressive manner. For the first four weeks of the protocol, those in the exercise group performed 3 sets of 10 reps for each exercise. In the following four weeks they increased the intensity and performed 3 sets of 5 reps. In the final 3 weeks of the study the exercises were performed in pairs of super sets. Each exercise was completed for 6 sets of 5 reps, where the first 4 sets had an increasing weight each set, and the last two sets had a decreasing weight (Cortez-Cooper et al., 2005).

While this is not a typical protocol, it is one of the few that implement sets with higher intensity weights lifted. However, the results showed this training resulted in detrimental effects on arterial stiffness. PWV significantly increased after the 11-week intervention as well as the carotid augmentation index. Interestingly, PWV also significantly increased in those in the control intervention. While a recent history of weightlifting was an exclusion criterion, women in both groups could be recreationally active. This may have played a role in the increased PWV seen in the control group, though it was noted activity levels did not change and the authors claimed this finding was due to spontaneous factors. The authors concluded that a short duration, progressive

high intensity increased measures of arterial stiffness in healthy young women (Cortez-Cooper et al., 2005).

Cortez-Cooper et al. also examined the effect that resistance training has on older adults in 2008. This study included both men and women aged between 40-80 years of age. This age range is where resistance training is especially recommended to slow muscle mass and bone mineral density loss due to aging and inactivity. Unlike their previous paper, this incorporated a more standard lifting protocol that lasted 11 weeks. Subjects in the lifting only protocol lifted 3 days a week and performed one set of 8-12 (70% 1RM). Those placed in the combined aerobic and resistance training lifted 2 days a week following the same program and also walked or cycled for 30-45 minutes at 60-75% of heart rate reserve on 2 days a week. They found there were no significant differences between pre and post PWV in either training group or the control group. While it is promising that there were no negative side effects of resistance training on the cardiovascular system in this older population, the study did utilize a more moderate training program as compared to their previous study which utilized a progressive training protocol (Cortez-Cooper et al., 2008).

Another study that incorporated a progressive prescription was run by Croymans et al. This study looked at obese, sedentary young men and the effect of resistance training on central blood pressures as well as PWV. This study was a pilot study and therefore used 8 control subjects and 28 subjects randomized into the training group. The training was 3 times a week for 12 weeks and progressed in intensity. Weeks 1-2 consisted of 2 sets of 12-15 reps, weeks 3-7 they performed 3 sets of 8-12, and weeks 8-12 they completed 1 set of 6-8 reps for each exercise. They found this training protocol

did not have a significant effect on PWV or AI (P= 0.43 and 0.34 respectively) (Croymans et al., 2014).

This finding contrasts with the previous study by Cortez-Cooper. In addition to this finding, they also saw significant decreases in multiple blood pressure measurements including cSBP (P=0.01), cDBP (P=0.02), brachial SBP (P=0.03) and brachial DBP (P=0.01). The study concluded that high-intensity, progressive RT program was able to improve central and peripheral blood pressures and had no negative effect on arterial stiffness. The changes in blood pressure were not trivial decreases, as cSBP went from a median value of 111.5 to 106.5mmHg, cDBP went from a median of 80.8 to 76.3mmHg and even larger changes were seen for the peripheral blood pressures. As stated above, this study appears to reach opposite conclusions when looking at the effect that a progressive, high intensity RT program has on central pulse wave measurements (Croymans et al., 2014).

So far all of the studies discussed have looked at a healthy population. Some studies included obese and sedentary subjects, but they were otherwise healthy when looking at the presence of CVD risk factors and other health issues. There has been meta-analysis performed on studies that have looked at the effect of resistance training on arterial stiffness in those who do have CVD and risk factors such as hypertension, obesity, and type two diabetes (Zhang et al., 2018). A meta-analysis by Zhang et al. found that for PWV there was no significant difference found after resistance training interventions when compared to control groups (MD=-0.26m/s, P= 0.27). This same analysis also looked at central blood pressures and found there were significant decreases for both central systolic and diastolic pressures in the resistance-trained groups compared

to controls (cSBP: MD= -7.62mmHg, P= 0.0000, cDBP: MD= -4mmHg, p= 0.001) (Zhang et al., 2018).

Another 2018 meta-analysis also looked at resistance training for those with CVD or at risk for CVD. The average sample size for the studies examined was 56 participants who were mostly older (52-69 years old). All studies had interventions lasting at least 8 weeks and most had training on 3 days a week. They found that after resistance training there was a nonsignificant decrease in PWV (MD= -0.4, p= 0.167) (Evans et al., 2018). Based on results from both of these meta-analyses it can be concluded that there is not a chronically increased burden placed on the heart from resistance training even in those with or at risk for cardiovascular disease. However, neither of these studies indicated the resistance training intensities that were used in all of the studies analyzed. When the individual studies were examined, it was found that most utilized a moderate to light intensity resistance training protocol.

There are few published articles that have examined high intensity weightlifting protocols and their effect on central hemodynamics and arterial stiffness. Although a recent review by Figueroa et al. did look at some high intensity protocols. The review looked at both high and low intensity resistance training on arterial stiffness and central blood pressure in both normotensive and hypertensive adults. When looking at higher intensity studies, they concluded the overall effect that high intensity resistance training has on PWV is either an increase or no effect in both young and old populations. When looking at the effect it has on both central and peripheral blood pressures it was shown that there is either a decrease or no change for higher intensity lifting (Figueroa et al., 2019).

The author notes there is still a need for more evidence when looking at protocols that incorporate intensities greater than 80% of 1RM. They also state there have been limited studies that look at the central BP effects of resistance training and there is not enough current evidence to conclude if different training characteristics (intensity, modalities, etc.) may impact the anti-hypertensive effect of training. The authors state that while the potential for adverse effects from high intensity resistance training exist, the majority of studies have shown it has no effect on arterial stiffness, and that training at any intensity has shown promising effects on both peripheral and central BPs (Figueroa et al., 2019). Based on this recent review, it seems there is still a need for clear evidence on high intensity resistance training.

One such study was done in 2019, by Werner et al. This study by Werner et al. is the most similar to the current study. It recruited 30 healthy male subjects aged 18-30 years old and underwent a 12-week intervention. It used 3 groups, a control group, a high-volume group, and a high intensity group. Those in the high-volume group performed 3-4 sets of 10-15 reps, and the high intensity group did 2-3 sets of 3-8 (80-90% 1RM). During the first two weeks they performed exercises on 3 days a week, but for the remainder of the study performed a split upper-lower body routine where the upper and lower body exercises were each performed 2-3 days a week. They found there were no significant differences in PWV or central systolic and diastolic pressures (Werner et al., 2019).

The major difference between this study and the current one is those who were included in the study sample. Werner's study chose to look at just young, healthy men due to younger women having "different baseline arterial stiffness than male

counterparts, potentially causing differences in primary outcomes" (Werner et al., 2019). The current study's main outcomes were to assess the effect of high intensity resistance training on obese and overweight, sedentary men and women. This population has been under studied in regard to cardiovascular adaptations to resistance training. Further, the age range of 18-55 was used in the current study, a more broad and representative age range as opposed to those used by Werner and Croymans who looked at younger individuals only (Croymans et al., 2014; Werner et al., 2019).

The current exercise guidelines recommend resistance training due to its benefits on body composition, glycemic control, and improved strength and quality of life (Williams et al., 2007). However, the current guidelines by the ACSM recommend 1 set of 8-12 reps (60-80% 1RM) (American College of Sports Medicine, Riebe, Ehrman, Ligouri, & Magal, 2018; Garber et al., 2011). Does this mean that those wishing to exercise at higher intensities may be exposing themselves to adverse outcomes, especially when looking at the cardiovascular system? Based on the current evidence discussed, it shows there is still need for more studies to be done concerning true high intensity resistance training protocols and the effect they have on central hemodynamics and arterial stiffness. Due to this lack of evidence, this study aimed to assess the effect that high-rep/low load and low-rep/high load had on measures of arterial stiffness and central pulse wave analysis.

CHAPTER 3

METHODS

Subjects

Sixty-two subjects were enrolled with the expectation that at least 33 subjects completed all aspects of the study. Potential participants were recruited by flyers hung around the downtown Phoenix area as well as through the use of online social platforms such as Nextdoor and Facebook. The participants were randomly assigned to one of 3 groups: High repetition/ low load resistance training, Low repetition/high load resistance training, and a Non-exercising control. At least 10 subjects were randomized into each group.

Inclusion Criteria

Subjects were included if they were 18-55 years of age, healthy, overweight or obese (BMI $\geq$ 25 kg/m^2), had no recent history of starting a structured exercise program or diet in the last 3 months, and were sedentary (verified with a pedometer).

Exclusion Criteria

Current smokers and/or recreational drug users (less than 6 months since quitting) were excluded from the study. Those who answered "yes" to any questions on the Physical Activity Readiness Questionnaire (PAR-Q) or who had any musculoskeletal contraindications to aerobic or resistance exercise were excluded. Those who were diagnosed with diabetes or heart disease or are taking medications for the treatment of diabetes, heart disease, and hypertension were excluded from the study. A history of anabolic steroid use in the previous 6 months was also an exclusion criterion. Lastly,

those who were unwilling to follow any aspect of the study protocol or those unwilling to commute to the research locations were excluded from the study.

Effect Size

The projected sample size was calculated based on the primary aim to assess changes in PWV between intervention and control groups. Based on previous literature, it was estimated that a decrease in PWV of 0.61 m/s could be seen at the end of 12 weeks of resistance training with no change in control subjects (Cortez-Cooper et al., 2008). However, it was chosen to use a conservative estimate of a 0.34 m/s decrease in PWV for this power analysis. Based on the estimate of a 0.34 m/s decrease it was found that a sample of 33 subjects would be sufficient to have 80% statistical power at an α of 0.05.

Study Design

Visit 1 (Screening)

Potential subjects came in for visit 1 which served as a screening visit after taking an online screening survey. Upon arrival subjects were given an informed consent and signed after it was thoroughly explained, and all questions were answered. Following this, subjects were given the PAR-Q and an additional medical health history questionnaire to assess for any exclusion criteria. Subjects then had their height and weight taken using a stadiometer and scale (Seca 284, Seca, Hamburg, Germany) and had BMI assessed to ensure inclusion criteria were met. Subjects also had their blood pressure taken after five minutes rest using an automated blood pressure cuff (HEM-907XL, Omron, Kyoto, Japan). Following this, subjects were then given either an accelerometer (SenseWear, Bodymedia, Pittsburgh, PA) or a pedometer (Fitbit, San Francisco, CA) to

wear for a week to assess for activity level. After this had been worn for a week, subjects were then scheduled for baseline testing.

Visit 2 and 3 or 39 (Baseline and Post Testing)

Upon arrival subjects had their height and weight taken again to ensure the BMI classification was still met. After this they were brought into a quiet, temperature-controlled room were PWV and PWA measurements were to be taken. Subjects rested in a supine position for at least 15 minutes prior to any measurements being taken. Subjects arrived in a fasted state (nothing but water after 10:00 PM the night before) and refrained from caffeine, alcohol, and dietary supplements for at least 24 hours before testing. Procedures followed were laid out by Van Bortel et al. (Van Bortel et al., 2012).

All female participants were tested during the follicular phase of the menstrual cycle. Previous articles published (Papaioannou et al., 2009; Robb et al., 2009) have suggested controlling for the menstrual cycle to optimize study design. Recently, a study by Priest et al. found that fluctuating sex hormones through the menstrual cycle did not have any significant effect on central arterial stiffness as measured by cfPWV (Priest et al., 2018). However, to reduce possible confounding variables all females in the current study were measured at the same point in the menstrual cycle.

Both PWA and PWV were measured using the SphygmoCor Xcel system (AtCor Medical, Sydney, NSW, Australia). This system has been validated by the previous SphygmoCor system and has been shown to be reproducible (Butlin et al., 2013; Hwang et al., 2014). When measuring PWA the Xcel system uses a cuff placed around the upper arm and measures the wave form at the brachial artery. The cuff first inflates to obtain the brachial blood pressures. Following this it inflates to a sub-diastolic pressure and

measures the volumetric displacement from each pulse wave. The system then uses the general transfer function to calculate the aortic waveform from the peripheral site (Butlin & Qasem, 2017). From the aortic waveform we are given CBP, AP, Aix, and Aix75.

cfPWV is performed by simultaneously obtaining carotid waveforms using applanation tonometry at the carotid artery and cuff-based waveforms obtained at the femoral artery at the upper thigh. The distances from the carotid site to the suprasternal notch and from the suprasternal notch to the top of the cuff are then measured in a straight line using a tape measure. Due to the additional distance from the top of the cuff to femoral pulse found near the groin, the distance from the top of the cuff to the femoral pulse is then subtracted from the total distance. The PWV is then calculated from the distance between the two sites (D) divided by the time delay between the two sites (t). Therefore, the formula is PWV= D/t (m/sec) where D is the distance between the two sites in meters and t is time in seconds.

Following the PWA and PWV measurements participants underwent a transthoracic echocardiogram in order to assess global longitudinal strain of the left ventricle. The echocardiogram was performed by a trained sonographer using the Terason uSmart 3300 system (Terason, Burlington, MA). Lagrangian strain was calculated using 2D speckle tracking and was analyzed using EchoInsight (Epsilon Imaging, Ann Arbor MI). In order to calculate GLS, 3 separate views were obtained, the apical 4 chamber view, apical 2 chamber, and apical long axis. Image acquisition and analysis followed the guidelines put forth by the EACVI/ASE/Industry taskforce (Voigt et al., 2015).

Exercise Intervention

Following baseline testing, subjects were randomized into either the high-rep/low load (HRLL), the low-rep/high load (LRHL) or the control group. Randomization was done using a software generated randomization table. Those who were randomized into the control protocol were asked to maintain their current level of physical activity for the duration of the 12-week intervention. Both of the intervention groups performed the same program other than the repetitions performed on each exercise. All exercise sessions took place at the Arizona State University Sundevil Fitness Center at the downtown Phoenix campus. Participants attended 3 sessions a week for 12 weeks and all sessions were supervised by trained personnel. Sessions lasted ~1-1.25 hours and were performed on nonconsecutive days.

Those who were randomized into the HRLL group performed 3 sets of 15 repetitions (~70% 1RM) to volitional fatigue and those in the LRHL group performed 3 sets of 5 repetitions (~90% 1RM) to volitional fatigue. 2-3 warm up sets at a submaximal load were completed before performing their 3 sets at the intended workload for each exercise. The program followed a linear periodization format and weight was increased on each exercise as they adapted to training overload in order to maintain training intensity. Exercise sessions cycled between two workout routines. Day 1 consisted of: leg press, bench press, cable row, step ups, seated leg extension, seated leg curls, and abdominal crunches. Day 2 consisted of: leg press, overhead press, back extensions, dumbbell lunges, latissimus dorsi pull downs, lying tricep extensions, and barbell bicep curls.

Repetition Maximum Testing

Repetition maximum testing took place during week 1, 6, and 12 and was used to ensure appropriate weight progression occurred as well as to test baseline and ending strength. Subjects performed 5 and 10 repetition max tests on the leg press, bench press, and latissimus dorsi pulldown. All 5 repetition max tests occurred on one day and the 10 repetition max tests were performed 48 hours after. Participants warmed up by performing 2 warmup sets of 5 or 10 repetitions with a low load based on individual ability. After these warmup sets weight was added to each subsequent set that the participant is able to complete the desired repetition amount with good form. If they fail before reaching the desired rep amount the highest weight lifted for the complete set will be used.

Statistical Analysis

Data were analyzed using SPSS software (version 25). Baseline differences in subject characteristics were analyzed using a one-way ANOVA. All pre-post data were analyzed using a linear mixed-model ANOVA in order to examine main effects between the group, time (pre-post), and group x time interactions. Sidak post hoc analysis was run if the omnibus f-test was significant. Correlations between changes in variables were assessed using bivariate linear correlations and Pearson correlation coefficients were analyzed. All p values were calculated based on a two-tailed hypothesis and alpha was set at 0.05.

CHAPTER 4

RESULTS

Baseline Characteristics

Twenty-one subjects completed the study intervention and completed both pre and post-testing (4 control, 11 LRHL, 6 HRLL). Recruitment for this master's thesis was cut short due to the COVID-19 outbreak which resulted in a complete cessation of all research activities at our institution. Table 1 outlines the participant baseline demographic information. No significant differences were seen between subject demographics at baseline ($p > 0.05$).

Table 1. Demographic information by group at baseline (mean values ± SD)

	Control	LRHL	HRLL	*p* value
Age (years)	38.5 ± 12.9	34.1 ± 10.9	35.0 ± 9.8	0.791
Sex (M/F)	2M, 2F	5M, 6F	2M, 4F	
Height (cm)	177.1 ± 13.5	172.8 ± 13.9	171.5 ± 9.3	0.78
Weight (kg)	86.7 ± 10.3	94.8 ± 25.4	103.3 ± 20.8	0.518
BMI (kg/m^2)	27.6 ± 1.6	31.3 ± 5.5	35.7 ± 10.5	0.209
Body fat (%)	40.5 ± 4.0	42.6 ± 6.9	41.4 ± 6.7	0.702

M and F represent male and female respectively
LRHL represents low repetition/high load
HRLL represents high repetition/low load

Pulse Wave Velocity

A significant group x time interaction was found when examining the group by visit changes in PWV (P= 0.024) as well as a trend towards change by visit, post lower than pre (P= 0.059). However, there were no significant group differences seen upon post hoc analysis due to the control group confounding the results found. I observed an unanticipated 0.5 m/s decrease seen in the control group due to unknown reasons (7.6 ± 0.8 vs. 7.1 ± 0.8). Similarly, there was a 0.4 m/s decrease seen in the HRLL intervention group (7.03 ± 0.67 vs. 6.59). When looking at the LRHL training group there was a nonsignificant increase of 0.2 m/s found after the intervention (6.7 ± 0.5 vs. 6.9 ± 0.5). Figure 1 depicts the changes in PWV observed between all 3 groups. Table 2 shows the changes observed for all variables examined.

Figure 1. Changes in PWV across all 3 intervention groups. Error bars 95% CI

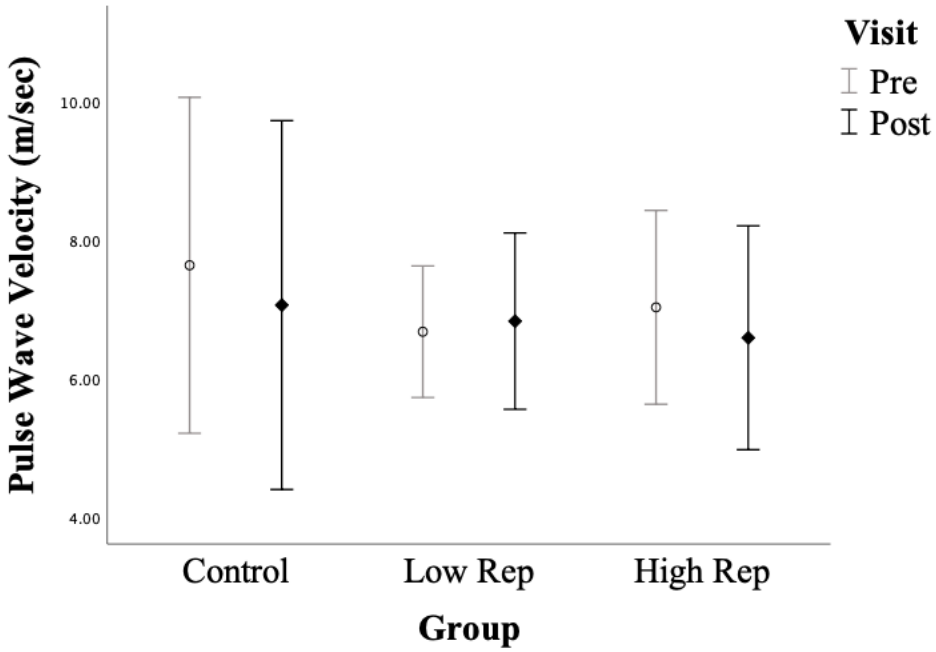


Table 2. Response to 12-week intervention within and between groups (mean ± SD)

Variable	Control n= 4		LRHL n= 11		HRLL n= 6		Fixed Effects		
	Pre	Post	Pre	Post	Pre	Post	Group	Time	Group x time
PWV (m/s)	7.6 ± 0.8	7.1 ± 0.8	6.7 ± 0.5	6.9 ± 0.5	7.0 ± 0.7	6.6 ± 0.7	0.802	0.059	0.024*
Aix75 (%)	6.3 ± 5.7	12.1 ± 5.7	21.0 ± 3.4	18.9 ± 3.4	16.8 ± 4.6	15.3 ± 4.6	0.237	0.717	0.266
Aix (%)	14.8 ± 5.7	19.9 ± 5.7	27.3 ± 3.4	25.9 ± 3.4	21.2 ± 4.7	20.1 ± 4.7	0.286	0.678	0.393
Central SBP (mmHg)	112 ± 5	113 ± 5	115 ± 3	116 ± 3	112 ± 4	115 ± 4	0.795	0.223	0.796
Central DBP (mmHg)	79 ± 3	80 ± 3	77 ± 2	78 ± 2	76 ± 3	78 ± 3	0.793	0.299	0.955
GLS (%)	-22 ± 1	-23 ± 1	-22 ± 1	-22 ± 1	-22 ± 1	-23 ±1	0.740	0.111	0.758
AP (mmHg)	6 ± 3	7 ± 3	12 ± 2	10 ± 2	8 ± 2	8 ± 2	0.242	0.883	0.285
Brachial SBP (mmHg)	123 ± 5	124 ± 5	126 ± 3	127 ± 3	123 ± 4	126 ± 4	0.871	0.388	0.861
Brachial DBP (mmHg)	78 ± 3	80 ± 3	75 ± 2	77 ± 2	75 ± 3	77 ± 3	0.767	0.241	0.994
Resting HR (bpm)	58 ± 3	59 ± 3	62 ± 3	61 ± 3	65 ± 3	64 ± 3	0.353	0.898	0.619
Body Fat (%)	39.5 ± 3.4	39.3 ± 3.4	41.1 ± 2.1	39.3 ± 2.1	43.2 ± 2.8	43.0 ± 2.8	0.633	0.011†	0.020*
BMI (kg/m^2)	27.6 ± 3.5	28.2 ± 3.5	31.3 ± 2.1	32.5 ± 2.1	35.8 ± 2.8	36.5 ± 2.8	0.192	0.172	0.885

* significant group x time interaction

† significant time interaction

Central Pressures

There were no significant differences found between intervention groups when looking at measures of central pressure ($P > 0.05$). Both Aix and Aix75 show nonsignificant increases in the control group 14.8 ± 5.7 vs. 19.9 ± 5.7 and 6.3 ± 5.7 vs. 12.1 ± 5.6 respectively. Minimal differences were observed in both of the training groups. Figures 2 and 3 depict the changes in Aix75 and Aix respectively. Figure 4 depicts the results found for central systolic pressure which showed minimal amounts of variation between the control (112 ± 4.8 vs. 113 ± 4.8), LRHL (115 ± 2.9 vs. 116 ± 2.9), and HRLL (112 ± 4.0 vs. 115 ± 4.0) groups. Overall no main effects or interaction effects were observed in any of the central pressure measurements.

Figure 2. Changes in Aix75 across all 3 intervention groups. Error bars 95% CI

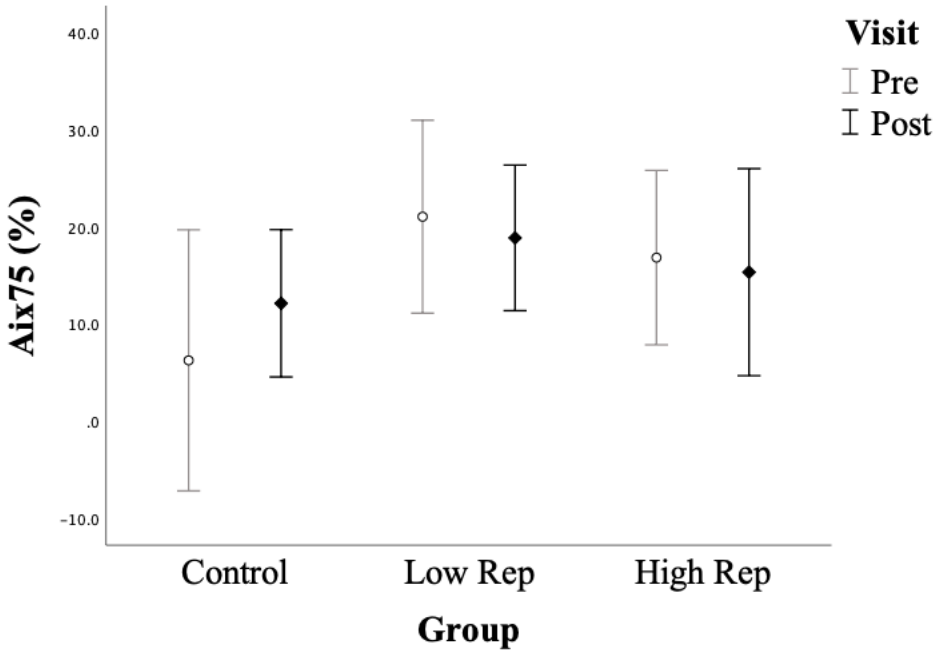


Figure 3. Changes in Aix across all 3 intervention groups. Error bars 95% CI

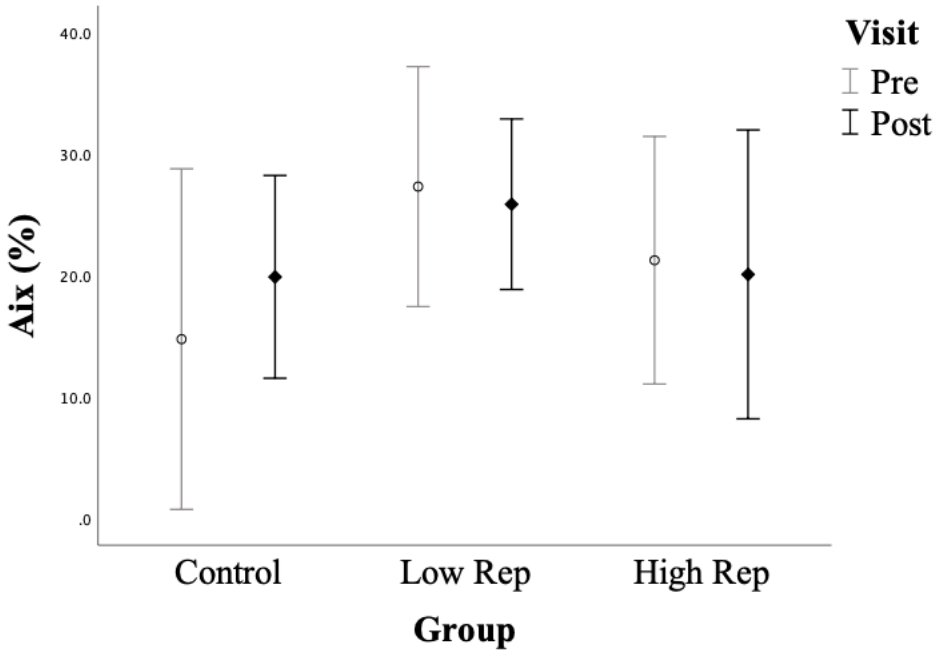
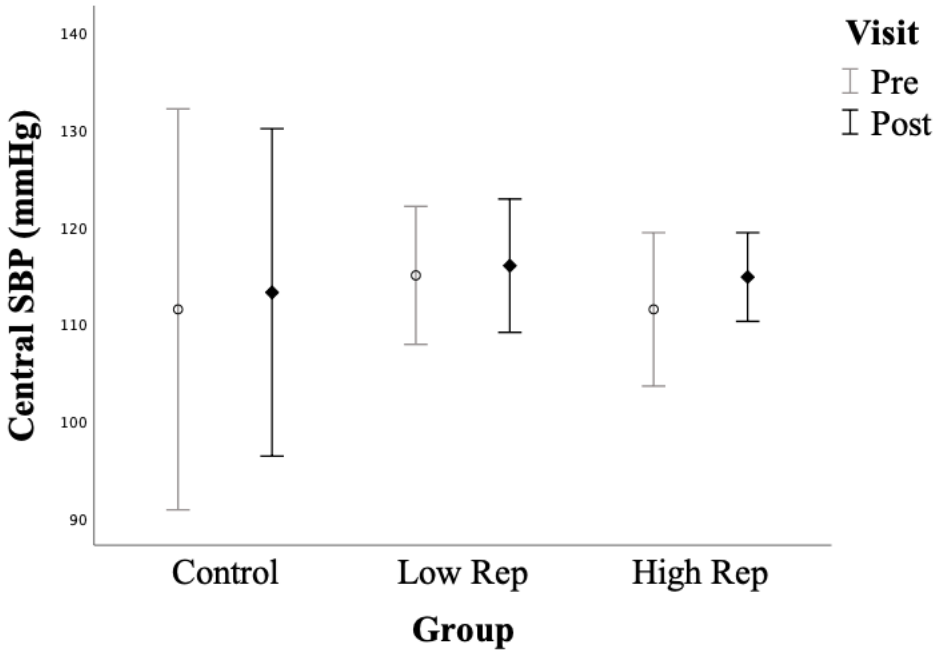


Figure 4. Changes in Central SBP across all 3 intervention groups. Error bars 95% CI



Heart Rate and Brachial Pressure

No significant differences were seen within or between groups after analysis ($p > 0.05$). No differences were seen in heart rate between groups or after intervention in control (58 ± 3.4 vs. 59 ± 3.4), LRHL (62 ± 2.1 vs. 61 ± 2.1), or HRLL (65 ± 2.8 vs. 64 ± 2.8). Similarly, no changes were seen in either the brachial systolic or diastolic blood pressures between or within a group.

Left Ventricular Global Longitudinal Strain

No significant interactions were seen within or between groups after analysis ($p > 0.05$). Minimal changes were observed between the 3 intervention groups. One of the tertiary aims of this study was also to assess any relationship between changes in GLS and markers of arterial stiffness. Changes in LV GLS were not significantly correlated with PWV, Aix75, or central SBP. The strongest correlation observed between these variables was the relationship between LV GLS and central SBP which had a $r^2 = 0.121$, which is still weak. Figures 5-8 depict the changes in LV GLS between intervention groups as well as the correlation between arterial stiffness measurements.

Figure 5. Changes in LV GLS across all 3 intervention groups. Error bars 95% CI

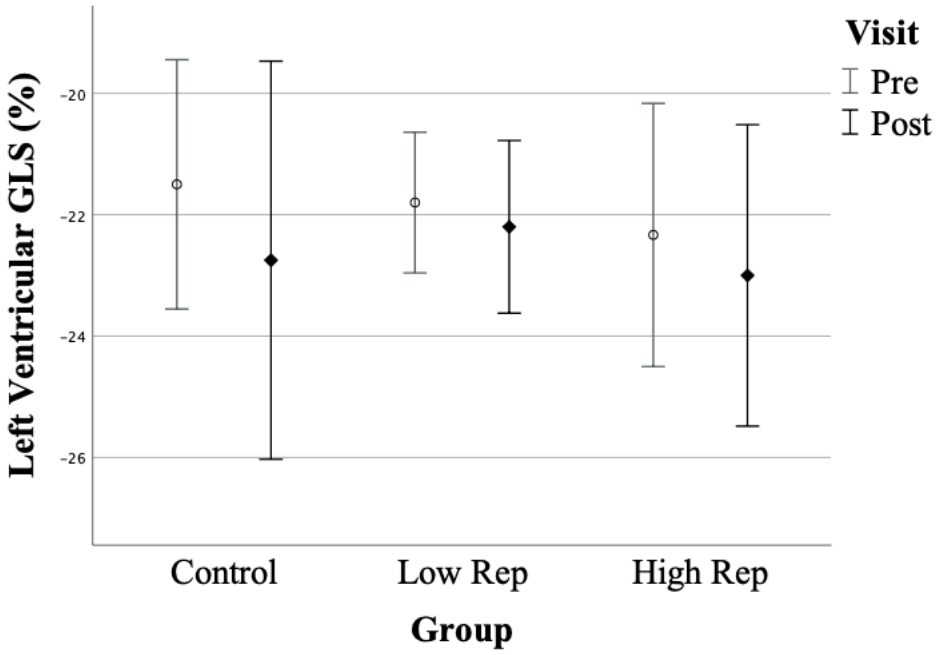


Figure 6. Correlation between delta LV GLS and delta PWV

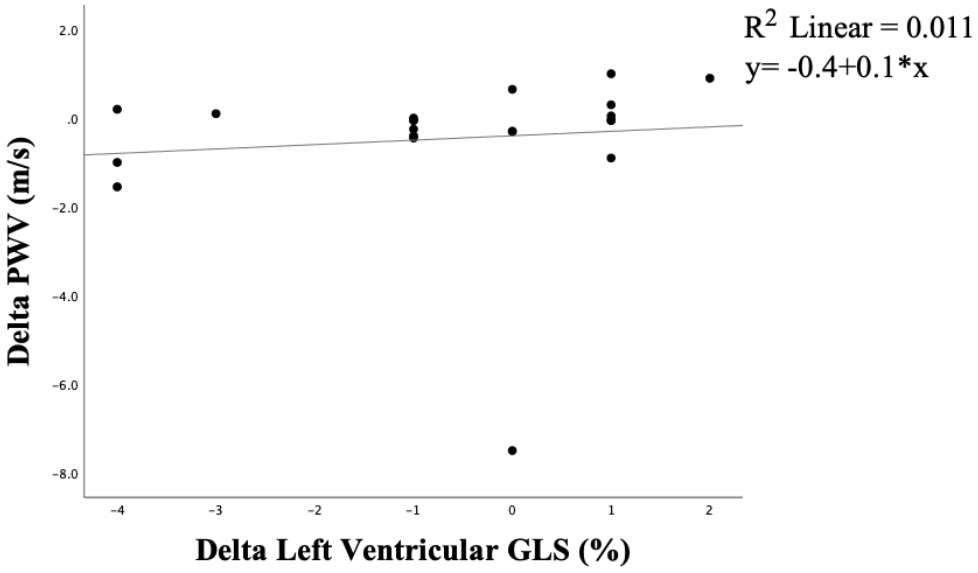


Figure 7. Correlation between delta LV GLS and delta Aix75

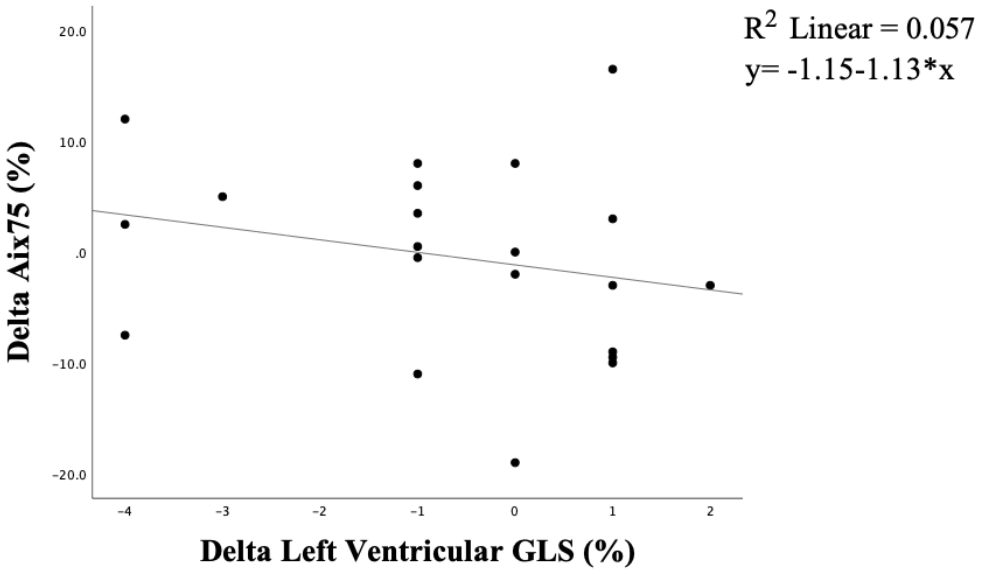
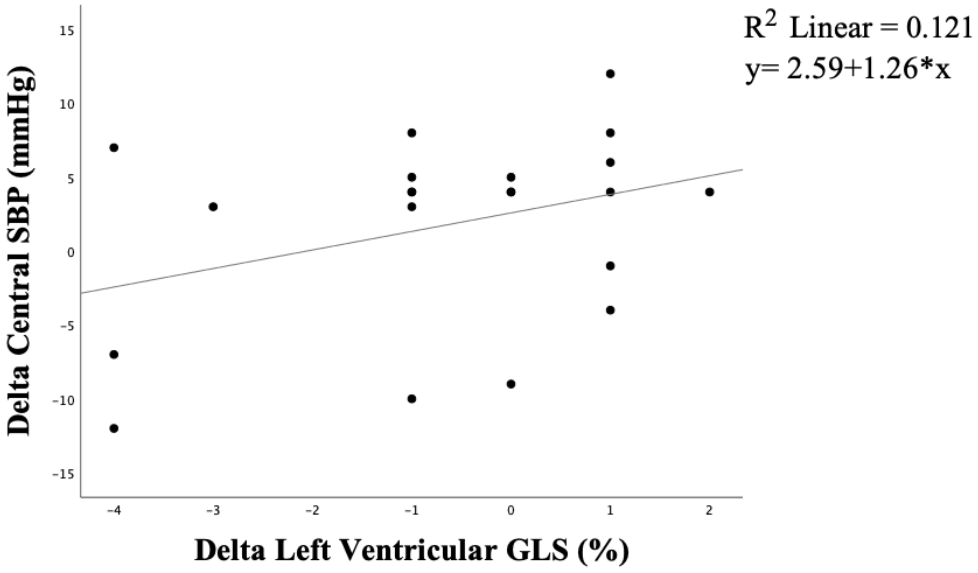


Figure 8. Correlation between delta LV GLS and delta central SBP



CHAPTER 5

DISCUSSION

The primary aim of this study was to assess the effect that either a high intensity or moderate intensity full body resistance training program performed on 3 days a week12 weeks would have on pulse wave velocity. After the 12-week intervention it was found that neither of the resistance training groups was superior to the control group for measures of arterial stiffness. One reason for this is due to the control group having an unanticipated outcome.

It was predicted that those in the control group would either have no changes in PWV or a slight increase over the course of the intervention. However, it was found that the control group had a large decrease in PWV (0.5 m/s), the biggest change seen across all groups. The LRHL group saw a small, nonsignificant increase (0.2 m/s) and the HRLL group saw a nonsignificant decrease (0.4 m/s). Due to this unanticipated result subject physical activity levels were examined in order to see if changes in activity could explain this. In the control group two of the four subjects saw minor changes in PWV, however two of them saw large reductions of 0.45 and 1.55 m/s. However, when physical activity levels were assessed, both of these subjects' overall average steps per day were reduced by 1,536 and 1099 steps respectively from the beginning to the end of the study. Based on our ability to gauge changes in physical activity, it shows that these subjects become less active, however this was only measured for 7 days and the beginning and end of the study. Subjects may have exercised during the control period and not reported this information.

It was hypothesized that both resistance training groups would not have any detrimental changes after the intervention. Based on the results it can be concluded that neither of the resistance training interventions had any negative effects on arterial stiffness. These results are similar to a study by Werner et al. (2019).

The study by Werner et al. found no statistically significant differences between control, high volume, and high intensity group after performing resistance training on 3-5 days a week for 12 weeks. The major difference in the intervention in this study and the one by Werner was that the high intensity group performed 3-8 repetitions compared to 5 repetitions in this study, and the high-volume group performed sets of 10-15 repetitions compared to 15 in this study. While there was more variation allowed in the Werner study, they also implemented slighter higher intensities allowing sets of 3 repetitions to be performed. This equates to 95% of 1RM as opposed to 87% used in this study. This difference in training intensities could explain the slight differences seen in the results between the two studies.

While both studies saw a nonsignificant increase in PWV, this study only saw a minor increase (0.2 m/s) while the study by Werner et al. observed a 1.0 m/s increase. While they stated this was nonsignificant, the meta-analysis by Ben-Shlomo et al. concluded that a 1 m/s increase in PWV resulted in a 7% increase in CVD event risk in older adults. Therefore, there is a chance for increased risk based on the results of Werner et al. (Ben-Shlomo et al., 2014; Werner et al., 2019). Based on this information it could be hypothesized that there is a resistance training intensity threshold, above which detrimental effects can be seen in arterial stiffness measures. Based on the results of these

two studies which implemented intensities of 87% and 95% of 1RM it could exist between these two intensities.

The results of this study differ from those from by Au et al. (2017) which found that there were significant decreases in PWV in both their low repetition and high repetition group (6.24 ± 0.56 vs. 5.77 ± 0.76 and 6.42 ± 0.7 vs. 5.72 ± 0.6 m/s respectively). One reason for this difference in results could be attributed to the difference in overall training intensities and repetitions used. Their low repetition group performed 3 sets of 8-12 repetitions and their high repetition group performed 3 sets of 20-25 repetitions. So, while they implemented a low repetition/high intensity training group, it was not as high intensity as the training regimen in this study, and those in that group could have been performing sets of 12, which is close to this studies high repetition group (Au et al., 2017).

This study saw minimal variations within and between groups regarding changes in central blood pressure. Between and within all groups there was only a 4 mmHg variation between all central systolic blood pressure measures (112-116 mmHg). There were no significant differences or interactions observed for central systolic or diastolic pressure. Similarly, there were no significant differences or interactions seen in Aix75 measures. This result differs from that seen by Croymans et al. which observed significant decreases in central systolic and diastolic blood pressures, brachial systolic and diastolic pressures, as well as Aix75 after 12 weeks of resistance training (Croymans et al., 2014).

The training intervention used by Croyman et al. differed significantly from the one used in this study. The training program in their study was a 12-week progressive

resistance training program. The first two weeks consisted of 2 sets of 12-15 repetitions, weeks 3-7 they performed 3 sets of 8-12, and weeks 8-12 they completed one set of 6-8 repetitions for each exercise (Croyman et al., 2014). This study used a set repetition and intensity level, and adjusted the weight being lifted as previous loads became easier. This progressive increase in training intensity may have been to reason for these differing results as both studies included sedentary, overweight and obese and non-hypertensive participants.

This study also performed an exploratory analysis to assess the effect these resistance training interventions had on left ventricular global longitudinal strain as well as to assess the relationship between changes in strain and measures of arterial stiffness. This study found no significant interactions by group, time, or group x time for LV GLS. There also were very weak relationships between the changes observed in strain and measures of PWV, Aix75, and central SBP (r^2= 0.011, 0.057, and 0.121 respectively).

The majority of studies that have incorporated global longitudinal strain measurements have involved clinical populations such as chemotherapy patients, those with heart failure and renal failure patients as well as in elite athletes in order to look at functional changes in the heart in these unique populations. No studies have assessed changes to global longitudinal strain in populations like the one used in this study. Future studies should be performed in order to assess the small functional changes to the myocardium that occur after exercise interventions in exercise naïve subjects in order to better understand any possible changes that may occur due to the onset of an exercise program.

CHAPTER 6

CONCLUSION

In conclusion the results show that 12-weeks of resistance training performed using high intensity or moderate intensity did not have any significant effect on measures of arterial stiffness including PWV, Aix75, central SBP, central DBP or any effect on peripheral blood pressure. In addition, no effect was seen on left ventricular global longitudinal strain and no relationships were observed between the changes in strain and the other variables assessed.

REFERENCES

American College of Sports Medicine, Riebe, D., Ehrman, J. K., Liguori, G., & Magal, M. (2018). *ACSM's guidelines for exercise testing and prescription*. /z-wcorg/.

Arnett, D. K., Blumenthal, R. S., Albert, M. A., Buroker, A. B., Goldberger, Z. D., Hahn, E. J., Himmelfarb, C. D., Khera, A., Lloyd-Jones, D., McEvoy, J. W., Michos, E. D., Miedema, M. D., Munoz, D., Smith, S. C. J., Virani, S. S., Williams, K. A. S., Yeboah, J., & Ziaeian, B. (2019). 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*, *140*(11), e596–e646. https://doi.org/10.1161/CIR.0000000000000678

Ashor, A. W., Lara, J., Siervo, M., Celis-Morales, C., & Mathers, J. C. (2014). Effects of exercise modalities on arterial stiffness and wave reflection: A systematic review and meta-analysis of randomized controlled trials. *PloS One*, *9*(10), e110034. https://doi.org/10.1371/journal.pone.0110034

Au, J. S., Oikawa, S. Y., Morton, R. W., Macdonald, M. J., & Phillips, S. M. (2017). Arterial Stiffness Is Reduced Regardless of Resistance Training Load in Young Men. *Medicine and Science in Sports and Exercise*, *49*(2), 342–348. https://doi.org/10.1249/MSS.0000000000001106

Ben-Shlomo, Y., Spears, M., Boustred, C., May, M., Anderson, S. G., Benjamin, E. J., Boutouyrie, P., Cameron, J., Chen, C.-H., Cruickshank, J. K., Hwang, S.-J., Lakatta, E. G., Laurent, S., Maldonado, J., Mitchell, G. F., Najjar, S. S., Newman, A. B., Ohishi, M., Pannier, B., … Wilkinson, I. B. (2014). Aortic pulse wave velocity improves cardiovascular event prediction: An individual participant meta-analysis of prospective observational data from 17,635 subjects. *Journal of the American College of Cardiology*, *63*(7), 636–646. https://doi.org/10.1016/j.jacc.2013.09.063

Butlin, M., & Qasem, A. (2017). Large Artery Stiffness Assessment Using SphygmoCor Technology. *Pulse (Basel, Switzerland)*, *4*(4), 180–192. https://doi.org/10.1159/000452448

Butlin, M., Qasem, A., Battista, F., Bozec, E., McEniery, C. M., Millet-Amaury, E., Pucci, G., Wilkinson, I. B., Schillaci, G., Boutouyrie, P., & Avolio, A. P. (2013). Carotid-femoral pulse wave velocity assessment using novel cuff-based techniques: Comparison with tonometric measurement. *Journal of Hypertension*, *31*(11), 2237–2243; discussion 2243. https://doi.org/10.1097/HJH.0b013e328363c789

Cortez-Cooper, M. Y., Anton, M. M., Devan, A. E., Neidre, D. B., Cook, J. N., & Tanaka, H. (2008). The effects of strength training on central arterial compliance in middle-aged and older adults. *European Journal of Cardiovascular Prevention and Rehabilitation : Official Journal of the European Society of Cardiology, Working Groups on*

Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology, *15*(2), 149–155. https://doi.org/10.1097/HJR.0b013e3282f02fe2

Cortez-Cooper, M. Y., DeVan, A. E., Anton, M. M., Farrar, R. P., Beckwith, K. A., Todd, J. S., & Tanaka, H. (2005). Effects of high intensity resistance training on arterial stiffness and wave reflection in women. *American Journal of Hypertension*, *18*(7), 930–934. https://doi.org/10.1016/j.amjhyper.2005.01.008

Croymans, D. M., Krell, S. L., Oh, C. S., Katiraie, M., Lam, C. Y., Harris, R. A., & Roberts, C. K. (2014). Effects of resistance training on central blood pressure in obese young men. *Journal of Human Hypertension*, *28*(3), 157–164. https://doi.org/10.1038/jhh.2013.81

D'Agostino, R. B. S., Vasan, R. S., Pencina, M. J., Wolf, P. A., Cobain, M., Massaro, J. M., & Kannel, W. B. (2008). General cardiovascular risk profile for use in primary care: The Framingham Heart Study. *Circulation*, *117*(6), 743–753. https://doi.org/10.1161/CIRCULATIONAHA.107.699579

Davies, J. I., & Struthers, A. D. (2005). Beyond blood pressure: Pulse wave analysis—A better way of assessing cardiovascular risk? *Future Cardiology*, *1*(1), 69–78. https://doi.org/10.1517/14796678.1.1.69

Doupis, J., Papanas, N., Cohen, A., McFarlan, L., & Horton, E. (2016). Pulse Wave Analysis by Applanation Tonometry for the Measurement of Arterial Stiffness. *The Open Cardiovascular Medicine Journal*, *10*, 188–195. https://doi.org/10.2174/1874192401610010188

Ernande, L., Bergerot, C., Rietzschel, E. R., De Buyzere, M. L., Thibault, H., Pignonblanc, P. G., Croisille, P., Ovize, M., Groisne, L., Moulin, P., Gillebert, T. C., & Derumeaux, G. (2011). Diastolic dysfunction in patients with type 2 diabetes mellitus: Is it really the first marker of diabetic cardiomyopathy? *Journal of the American Society of Echocardiography : Official Publication of the American Society of Echocardiography*, *24*(11), 1268-1275.e1. https://doi.org/10.1016/j.echo.2011.07.017

Evans, W., Willey, Q., Hanson, E. D., & Stoner, L. (2018). Effects of Resistance Training on Arterial Stiffness in Persons at Risk for Cardiovascular Disease: A Meta-analysis. *Sports Medicine (Auckland, N.Z.)*, *48*(12), 2785–2795. https://doi.org/10.1007/s40279-018-1001-6

Figueroa, A., Okamoto, T., Jaime, S. J., & Fahs, C. A. (2019). Impact of high- and low-intensity resistance training on arterial stiffness and blood pressure in adults across the lifespan: A review. *Pflugers Archiv : European Journal of Physiology*, *471*(3), 467–478. https://doi.org/10.1007/s00424-018-2235-8

Hirata, K., Kawakami, M., & O'Rourke, M. F. (2006). Pulse wave analysis and pulse wave velocity: A review of blood pressure interpretation 100 years after Korotkov. *Circulation Journal : Official Journal of the Japanese Circulation Society*, *70*(10), 1231–1239.

Hwang, M. H., Yoo, J. K., Kim, H. K., Hwang, C. L., Mackay, K., Hemstreet, O., Nichols, W. W., & Christou, D. D. (2014). Validity and reliability of aortic pulse wave velocity and augmentation index determined by the new cuff-based SphygmoCor Xcel. *Journal of Human Hypertension*, *28*(8), 475–481. https://doi.org/10.1038/jhh.2013.144

Karamanoglu, M., O'Rourke, M. F., Avolio, A. P., & Kelly, R. P. (1993). An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man. *European Heart Journal*, *14*(2), 160–167. https://doi.org/10.1093/eurheartj/14.2.160

Laurent, S., Cockcroft, J., Van Bortel, L., Boutouyrie, P., Giannattasio, C., Hayoz, D., Pannier, B., Vlachopoulos, C., Wilkinson, I., & Struijker-Boudier, H. (2006). Expert consensus document on arterial stiffness: Methodological issues and clinical applications. *European Heart Journal*, *27*(21), 2588–2605. https://doi.org/10.1093/eurheartj/ehl254

Li, Y., Hanssen, H., Cordes, M., Rossmeissl, A., Endes, S., & Schmidt-Trucksass, A. (2015). Aerobic, resistance and combined exercise training on arterial stiffness in normotensive and hypertensive adults: A review. *European Journal of Sport Science*, *15*(5), 443–457. https://doi.org/10.1080/17461391.2014.955129

Miyachi, M. (2013). Effects of resistance training on arterial stiffness: A meta-analysis. *British Journal of Sports Medicine*, *47*(6), 393–396. https://doi.org/10.1136/bjsports-2012-090488

Miyachi, M., Kawano, H., Sugawara, J., Takahashi, K., Hayashi, K., Yamazaki, K., Tabata, I., & Tanaka, H. (2004). Unfavorable effects of resistance training on central arterial compliance: A randomized intervention study. *Circulation*, *110*(18), 2858–2863. https://doi.org/10.1161/01.CIR.0000146380.08401.99

Morra, E. A., Zaniqueli, D., Rodrigues, S. L., El-Aouar, L. M., Lunz, W., Mill, J. G., & Carletti, L. (2014). Long-term intense resistance training in men is associated with preserved cardiac structure/function, decreased aortic stiffness, and lower central augmentation pressure. *Journal of Hypertension*, *32*(2), 286–293. https://doi.org/10.1097/HJH.0000000000000035

Noon, J. P. (2009). The arterial pulse wave and vascular compliance. *Progress in Cardiovascular Nursing*, *24*(2), 53–58. https://doi.org/10.1111/j.1751-7117.2009.00032.x

Nurnberger, J., Keflioglu-Scheiber, A., Opazo Saez, A. M., Wenzel, R. R., Philipp, T., & Schafers, R. F. (2002). Augmentation index is associated with cardiovascular risk. *Journal of Hypertension*, *20*(12), 2407–2414. https://doi.org/10.1097/00004872-200212000-00020

O'Rourke, M. F., Staessen, J. A., Vlachopoulos, C., Duprez, D., & Plante, G. E. (2002). Clinical applications of arterial stiffness; definitions and reference values. *American Journal of Hypertension*, *15*(5), 426–444. https://doi.org/10.1016/s0895-7061(01)02319-6

Papaioannou, T. G., Stamatelopoulos, K. S., Georgiopoulos, G., Vlachopoulos, C., Georgiou, S., Lykka, M., Lambrinoudaki, I., Papamichael, C. M., & Stefanadis, C. I. (2009). Arterial wave reflections during the menstrual cycle of healthy women: A reproducibility study. *Hypertension (Dallas, Tex. : 1979)*, *54*(5), 1021–1027. https://doi.org/10.1161/HYPERTENSIONAHA.109.137703

Potter, E., & Marwick, T. H. (2018). Assessment of Left Ventricular Function by Echocardiography: The Case for Routinely Adding Global Longitudinal Strain to Ejection Fraction. *JACC. Cardiovascular Imaging*, *11*(2 Pt 1), 260–274. https://doi.org/10.1016/j.jcmg.2017.11.017

Priest, S. E., Shenouda, N., & MacDonald, M. J. (2018). Effect of sex, menstrual cycle phase, and monophasic oral contraceptive pill use on local and central arterial stiffness in young adults. *American Journal of Physiology. Heart and Circulatory Physiology*, *315*(2), H357–H365. https://doi.org/10.1152/ajpheart.00039.2018

Robb, A. O., Mills, N. L., Din, J. N., Smith, I. B. J., Paterson, F., Newby, D. E., & Denison, F. C. (2009). Influence of the menstrual cycle, pregnancy, and preeclampsia on arterial stiffness. *Hypertension (Dallas, Tex. : 1979)*, *53*(6), 952–958. https://doi.org/10.1161/HYPERTENSIONAHA.109.130898

Shirwany, N. A., & Zou, M. (2010). Arterial stiffness: A brief review. *Acta Pharmacologica Sinica*, *31*(10), 1267–1276. https://doi.org/10.1038/aps.2010.123

Stanton, T., Leano, R., & Marwick, T. H. (2009). Prediction of all-cause mortality from global longitudinal speckle strain: Comparison with ejection fraction and wall motion scoring. *Circulation. Cardiovascular Imaging*, *2*(5), 356–364. https://doi.org/10.1161/CIRCIMAGING.109.862334

Stoner, L., Faulkner, J., Lowe, A., M Lambrick, D., M Young, J., Love, R., & S Rowlands, D. (2014). Should the augmentation index be normalized to heart rate? *Journal of Atherosclerosis and Thrombosis*, *21*(1), 11–16. https://doi.org/10.5551/jat.20008

Szelenyi, Z., Fazakas, A., Szenasi, G., Tegze, N., Fekete, B., Molvarec, A., Hadusfalvy-Sudar, S., Janosi, O., Kiss, M., Karadi, I., & Vereckei, A. (2015). The mechanism of reduced longitudinal left ventricular systolic function in hypertensive patients with normal ejection fraction. *Journal of Hypertension*, *33*(9), 1962–1969; discussion 1969. https://doi.org/10.1097/HJH.0000000000000624

Van Bortel, L. M., Laurent, S., Boutouyrie, P., Chowienczyk, P., Cruickshank, J. K., De Backer, T., Filipovsky, J., Huybrechts, S., Mattace-Raso, F. U. S., Protogerou, A. D., Schillaci, G., Segers, P., Vermeersch, S., & Weber, T. (2012). Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *Journal of Hypertension*, *30*(3), 445–448. https://doi.org/10.1097/HJH.0b013e32834fa8b0

Voigt, J.-U., Pedrizzetti, G., Lysyansky, P., Marwick, T. H., Houle, H., Baumann, R., Pedri, S., Ito, Y., Abe, Y., Metz, S., Song, J. H., Hamilton, J., Sengupta, P. P., Kolias, T. J., d'Hooge, J., Aurigemma, G. P., Thomas, J. D., & Badano, L. P. (2015). Definitions for a common standard for 2D speckle tracking echocardiography: Consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *European Heart Journal Cardiovascular Imaging*, *16*(1), 1–11. https://doi.org/10.1093/ehjci/jeu184

Weber, T., Auer, J., O'Rourke, M. F., Kvas, E., Lassnig, E., Berent, R., & Eber, B. (2004). Arterial stiffness, wave reflections, and the risk of coronary artery disease. *Circulation*, *109*(2), 184–189. https://doi.org/10.1161/01.CIR.0000105767.94169.E3

Werner, T. J., Pellinger, T. K., Rosette, V. D., & Ortlip, A. T. (2019). Effects of a 12-Week Resistance Training Program on Arterial Stiffness: A Randomized Controlled Trial. *Journal of Strength and Conditioning Research*. https://doi.org/10.1519/JSC.0000000000003331

Williams, M. A., Haskell, W. L., Ades, P. A., Amsterdam, E. A., Bittner, V., Franklin, B. A., Gulanick, M., Laing, S. T., & Stewart, K. J. (2007). Resistance exercise in individuals with and without cardiovascular disease: 2007 update: A scientific statement from the American Heart Association Council on Clinical Cardiology and Council on Nutrition, Physical Activity, and Metabolism. *Circulation*, *116*(5), 572–584. https://doi.org/10.1161/CIRCULATIONAHA.107.185214

Willum-Hansen, T., Staessen, J. A., Torp-Pedersen, C., Rasmussen, S., Thijs, L., Ibsen, H., & Jeppesen, J. (2006). Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation*, *113*(5), 664–670. https://doi.org/10.1161/CIRCULATIONAHA.105.579342

Zhang, Y., Qi, L., Xu, L., Sun, X., Liu, W., Zhou, S., van de Vosse, F., & Greenwald, S. E. (2018). Effects of exercise modalities on central hemodynamics, arterial stiffness and cardiac function in cardiovascular disease: Systematic review and meta-analysis of randomized controlled trials. *PloS One*, *13*(7), e0200829. https://doi.org/10.1371/journal.pone.0200829

Zhong, Q., Hu, M.-J., Cui, Y.-J., Liang, L., Zhou, M.-M., Yang, Y.-W., & Huang, F. (2018). Carotid-Femoral Pulse Wave Velocity in the Prediction of Cardiovascular Events and Mortality: An Updated Systematic Review and Meta-Analysis. *Angiology*, *69*(7), 617–629. https://doi.org/10.1177/0003319717742544

APPENDIX A

ARIZONA STATE UNIVERISTY INSTITUTIONAL REVIEW BOARD APPROVAL

ASU Knowledge Enterprise Development

APPROVAL:CONTINUATION

Siddhartha Angadi
Exercise Science and Health Promotion 602/827-2254
sangadi@asu.edu

Dear Siddhartha Angadi:

On 12/30/2019 the ASU IRB reviewed the following protocol:

Type of Review:	Continuing Review
Title:	Resistance Training and Vascular Health Study
Investigator:	Siddhartha Angadi
IRB ID:	STUDY00006617
Category of review:	
Funding:	Name: Graduate College (GRAD), Funding Source ID: GPSA
Grant Title:	None
Grant ID:	None
Documents Reviewed:	• Flyer with QR code, Category: Recruitment Materials; • Informed Consent, Category: Consent Form; • Flyer, Category: Recruitment Materials;

The IRB approved the protocol from 12/30/2019 to 5/10/2020 inclusive. Three weeks before 5/10/2020 you are to submit a completed Continuing Review application and required attachments to request continuing approval or closure.

If continuing review approval is not granted before the expiration date of 5/10/2020 approval of this protocol expires on that date. When consent is appropriate, you must use final, watermarked versions available under the “Documents” tab in ERA-IRB.

In conducting this protocol you are required to follow the requirements listed in the INVESTIGATOR MANUAL (HRP-103).

Sincerely,

IRB Administrator