2018

The Effects of High Intensity Interval Training on Arterial Health

James Smith

Follow this and additional works at: <https://researchrepository.wvu.edu/etd>

Recommended Citation

Smith, James, "The Effects of High Intensity Interval Training on Arterial Health" (2018). *Graduate Theses, Dissertations, and Problem Reports*. 7257.

<https://researchrepository.wvu.edu/etd/7257>

This Thesis is protected by copyright and/or related rights. It has been brought to you by the The Research Repository @ WVU with permission from the rights-holder(s). You are free to use this Thesis in any way that is permitted by the copyright and related rights legislation that applies to your use. For other uses you must obtain permission from the rights-holder(s) directly, unless additional rights are indicated by a Creative Commons license in the record and/ or on the work itself. This Thesis has been accepted for inclusion in WVU Graduate Theses, Dissertations, and Problem Reports collection by an authorized administrator of The Research Repository @ WVU. For more information, please contact researchrepository@mail.wvu.edu.

The Effects of High Intensity Interval Training on Arterial Health

James Smith

Thesis submitted to the School of Medicine at West Virginia University
In partial fulfillment of the requirements for the degree of: Master of Science in Exercise
Physiology

Paul D. Chantler, Ph.D., Committee Chair

Randall W. Bryner, Ed.D

David A. Donley, M.S.

Emidio E. Pistilli, Ph.D

Department of Exercise Physiology

Morgantown, WV 2018

Keywords: Cardiovascular disease, arterial stiffness, aerobic exercise, pulse wave
velocity

Copyright 2018 James Smith

Abstract

The Effects of High Intensity Interval Training on Arterial Health

James Smith

Cardiovascular disease (CVD) is the leading cause of mortality in the world with over 600,000 deaths annually in the United States. Annually, physical inactivity costs \$68 billion to cover medical bills, productivity losses, and results in over 17 million deaths globally. While some factors that contribute to CVD by impacting arterial stiffness can be delayed or accelerated, such as obesity, poor diet, physical inactivity, and metabolic diseases, factors such as biological aging cannot be avoided. Exercise is an effective stimulus for normal vascular functioning and homeostasis. The American Heart Association recommends moderate intensity exercise (50-70% predicted maximal heart rate) at least 30 minutes a day, most days of the week, to reduce the risk of cardiovascular incidents and risk. Unfortunately, 50% of individuals disengage from an exercise program within the first six months of starting, stating time to be the greatest barrier, warranting shorter alternatives. However, it is unknown what the optimal duration and intensity is required to help prevent or manage cardiovascular disorders. We tested the following hypotheses: 1) Individuals who exercise for 8 weeks in the HIIT training group will elicit greater improvements in arterial stiffness compared to those in the CT group and 2) Individuals who exercise for 8 weeks in the HIIT training group will elicit superior arterial and cardiac adaptations, as well as a larger increase in exercise performance than those in the LV-HIIT group.

Acknowledgements

I would like to express my appreciation to my mentor Dr. Paul Chantler. When I was first arrived to WVU I struggled with the demands of graduate school and my classes. It was a steep learning curve, but he did not give up on me. With some tough love, I was able to make great strides forward for my future. Thank you Dr. Chantler for giving me multiple chances and believing in my potential and accepting me into your lab. It is because of you and everything I have learned at WVU why I'm moving forward in life.

I also would like to extend my gratitude to the Human Performance Lab and especially Mr. David Donley and Mr. Danny Bonner. You both helped me with almost every stress test, from scheduling them all to teaching me some of the most fundamental concepts in clinical exercise physiology. Thank you for putting up with my many questions and having patience with me during the beginning stages of this thesis. I was able to transition subjects in the study quickly and smoothly due to both of you making the availability in your schedules. I also want to thank Kent Marshall for assisting in some of the stress tests when scheduling subjects became more difficult during specific time periods.

Thank you to WVU Medicine Wellness Center for offering me a graduate assistantship and financially supporting me throughout my time at WVU. I have enjoyed the experiences and the memories that have occurred along the way. I would also like to thank my remaining thesis committee members Dr. Bryner and Dr. Pistilli for agreeing to be part of my thesis and offering their expertise and insight.

Lastly, I would like to thank my father for giving me the opportunity to attend college and be on the path I am today. It was because of your hard work, sacrifices, and patience that I am where I am today and able to have a bright future ahead of me. Thank you for all you have done throughout my life and helping me have a brighter future for myself.

Table of Contents

Abstract.....	ii
Abbreviations	v
INTRODUCTION.....	
1.1. Purpose	2
1.2. Specific Aims and Hypothesis	3
1.3. Background and Significance	4
REVIEW OF LITERATURE.....	
2.1. Cardiovascular Health	9
2.1.1. Normal Cardiovascular Function	9
2.1.2. Normal Endothelial Function	10
2.1.3. Cardiovascular Dysfunction.....	13
2.1.4. Vascular Dysfunction.....	17
2.1.5. Endothelial Function Measurements	19
2.1.6. Exercise for vascular dysfunction.....	23
2.1.7. HIIT versus MICT.....	24
2.2. Arterial Stiffness	28
2.2.1. Aging	28
2.2.2. Hypertension	29
2.2.3. Diabetes	31
2.2.4. Body composition	32
2.2.5. Physical Inactivity	33
METHODS.....	
3.1. Experimental design	36
3.2. Training protocol	38
3.3. Experimental measures	39
3.3.1. Pulse Wave Velocity.....	39
3.3.2. Pulse Wave Analysis.....	40
3.3.3. Carotid Intima Media Thickness	40
3.4. Statistics	41
RESULTS.....	
4.1. Effects of Aerobic Exercise on Arterial Stiffness.....	43
GENERAL DISCUSSION.....	
5.1. Discussion	50
5.2. Future Directions	54
5.3. Limitations	55

Abbreviations

Cardiovascular Disease (CVD)

Endothelial Nitric Oxide Synthase (eNOS)

Left Ventricle (LV)

Nitric Oxide (NO)

High Intensity Interval Training (HIIT)

Moderate Intensity Continuous Training (MICT)

Continuous Training (CT)

Low-Volume High Intensity Interval Training (LV-HIIT)

Blood Pressure (BP)

Systolic Blood Pressure (SBP)

Diastolic Blood Pressure (DBP)

Central Systolic Blood Pressure (cSBP)

Central Diastolic Blood Pressure (cDBP)

Heart Rate Reserve (HRR)

Heart Rate (HR)

Beats Per Minute (BPM)

Aortic Pulse Wave Velocity (PWV)

Carotid-Femoral Pulse Wave Velocity (cfPWV)

Pulse Wave Analysis (PWA)

Augmentation Index (AIx)

Augmentation index standardized at HR of 75 bpm (Aix@HR75)

Augmentation Pressure (AP)

Body Mass Index (BMI)

Human Performance Lab (HPL)

Carotid Intima Media Thickness (cIMT)

Sub Endocardial Viability Ration (SEVR)

Cardiorespiratory Fitness (CRF)

Respiratory Exchange Ratio (RER)

Chapter 1

Introduction

1.1. Purpose

Arterial stiffness is defined as the elasticity and compliancy of the blood vessels within the vasculature. With normal aging, arteries naturally grow stiffer due to fracture and fragmentation of elastin proteins and the deposition of collagen in their place¹. Under normal conditions, central arteries act as a conduit vessel to direct the flow of blood to the periphery and as a cushion to buffer the pulsatile ejection of blood from the left ventricle (LV), allowing for adequate perfusion of organs². In individuals with increased arterial stiffness, perfusion of the organs can be decreased which will result in an increased risk of cardiovascular incidents³.

Exercise is an effective stimulus for normal vascular functioning and homeostasis⁴. The American Heart Association recommends moderate intensity exercise (50-70% predicted maximal heart rate) at least 30 minutes a day, most days of the week, to reduce the risk of cardiovascular incidents and risk⁵. Exercise improves cardiorespiratory fitness levels (CRF), which are inversely correlated with CVD and all-cause mortality rates⁶. Unfortunately, 50% of individuals disengage from an exercise program within the first six months of starting, stating time to be the greatest barrier⁷.

High intensity interval training (HIIT), which involves repeated bouts of vigorous exercise interspersed with lower intensities of “active recovery”, has proven to be an effective and time friendly alternative to traditional exercise guidelines. It has been reported that HIIT training elicits physiological remodeling similar to that of moderate intensity continuous training (MICT)

in healthy adults, with less time commitment and training volume ^{8,9}. Specifically, HIIT has shown to induce increases in muscle metabolism ⁹, peak oxygen uptake (VO₂ peak) ¹⁰, and endothelial function ¹¹ at comparable, or even greater levels compared to MICT. However, while HIIT training has proven to be comparable to that of MICT and promote better adherence to exercise ⁷, no optimal time duration or intensity of exercise has yet to be established.

1.2. Specific Aims and Hypothesis

Specific Aim #1a: Determine the effects of an 8-week aerobic exercise program on arterial stiffness in healthy, sedentary individuals.

- Hypothesis #1: Individuals who exercise for 8 weeks in the HIIT training group will elicit greater improvements in arterial stiffness compared to those in the CT group.

Specific Aim #1b: Determine the effects of an 8-week Low Volume High Intensity Interval Training (LV-HIIT) aerobic exercise training program versus 8 weeks of HIIT aerobic exercise program.

- Hypothesis #2: Individuals who exercise for 8 weeks in the HIIT training group will elicit superior arterial and cardiac adaptations, as well as a larger increase in exercise performance than those in the LV-HIIT group.

1.3. Background and Significance

Cardiovascular disease (CVD) is the leading cause of mortality in the world with over 600,000 deaths annually in the United States ¹². Annually, physical inactivity costs \$68 billion to cover medical bills, productivity losses, and results in over 17 million deaths globally ¹². While some factors that contribute to CVD by impacting arterial stiffness can be delayed or accelerated, such as obesity, poor diet, physical inactivity, and metabolic diseases, factors such as biological aging cannot be avoided.

Aging leads to a host of changes in the cardiovascular system, primarily increasing arterial stiffness, or arteriosclerosis. Principal causes of arterial stiffness are functional and structural changes observed within the vasculature, such as large arteries like the aortic and carotid arteries compared to smaller, more muscular arteries in the periphery such as the brachial or femoral arteries. Arterial stiffness is identified as an independent risk factor for the prediction of future cardiovascular incidents and disease due to its ability to illustrate decreased capabilities of an artery in response to pressure changes, such as constriction or relaxation. While generalized stiffening of the vasculature is known to occur with normal aging, central arterial stiffening is now recognized as an important consequence of aging that can contribute to vascular diseases such as systolic hypertension ¹³, stroke ¹⁴, and heart failure ¹⁴.

The arterial system can be thought of as two sub systems: large elastic arteries (ex. aorta and carotid) and muscular arteries (ex. brachial and femoral). Large elastic arteries store blood ejected from the heart during systole and recoil during diastole, which expels blood to the peripheral circulation, ensuring a steady flow of blood during both cardiac cycles. Muscular arteries alter vascular tone which allows the regulation of pressure wave velocities from the larger vessels upstream ¹⁵. This function of the muscular arteries is important in regulating the concept of the “reflected wave”.

When the heart contracts, a pressure wave is generated and propagated along the vascular tree at a relatively low velocity ¹⁶. As the wave travels throughout the vasculature, it encounters regions of varying impedance mismatches due to different properties of the vascular walls. These mismatches amplify the wave forward, but also cause a partial wave reflection back towards the heart. Collectively, all the partial reflected waves are summated into an overall, backward traveling “reflected wave” that propagates towards the heart and returns during late systole and early diastole ¹⁷. This reflected wave offers a boost to the diastolic filling pressure at the root of the aorta, which enhances coronary flow and helps to produce a more forceful contraction during the next cardiac cycle ¹⁷.

However, with increases in arterial stiffness, the properties of the pulse waves are changed. As an individual ages, the aorta stiffens and dilates ¹⁸. Additionally, the aortic wall thickens independent of atherosclerotic disease, heavily due to intimal thickening ¹⁹, elastin fragmentation and depletion²⁰, and collagen deposition ²⁰. Summated, these changes cause an

increase in stiffness, as well as an increase in pressure in the central arteries ²⁰, thus an increase of the workload on the LV. This causes a decrease in the diastolic filling pressure, decreasing the perfusion of the coronary arteries and reduces the diastolic filling duration of the cardiac cycle

².

Figure 1.1: Comparison of a healthy artery versus a stiff artery during cardiac cycles. (Laurent and Boutouyrie, 2015)

Aerobic exercise has been proven to reduce large elastic arterial stiffness in a plethora of studies, including healthy, young, middle, and older aged individuals ^{21,22} and those with cardiovascular risk factors ²³. However, it is not known the specific modality, intensity, or duration to help prevent or manage cardiovascular disorders ²⁴. In healthy individuals, longer duration and higher intensity is required for measurable physiological changes while older and diseased individuals receive beneficial adaptations from less intense exercise programs ²⁵.

MICT is renowned for being the preferred method of training for patients with CVD and helping to prevent CVD ²⁶. However, HIIT has grown as a popular method of exercise due to its lower time commitment and comparable or even superior physiological benefits ²⁷. HIIT is defined as brief, intermittent bursts of high intensity exercise, interspersed with periods of rest or lower intensity exercise known as “active recovery”. HIIT has long been used as a method of improving athletic performance in elite athletes for decades, but within the past two-three decades, has grown popular among the general population. HIIT has shown to not only be effective in clinical populations ^{10,23} for vascular measurements, but also for CRF levels ²⁶ and overall myocardium function ²⁸ given a lower time commitment compared to MICT. Given that lack of time is the largest barrier to exercise, HIIT may be an attractive, alternative method of exercise for the general population in combating CVD risks and overall mortality.

Chapter 2

Review of Literature

2.1. Vascular Health

2.1.1. Normal Cardiovascular Function

Two distinct components of the arterial system are to act as a conduit and a cushion. When the LV contracts it delivers blood throughout the body via capillaries in organs and tissues, but also cushions pulsations from the heart ². Interestingly, the flow of blood is continuous, even, and uninterrupted throughout the vasculature, even though the pumping ability of the heart is intermittent ². This is possible due to the elastic nature of the large central arteries acting as a pressure reservoir and “storing” blood during the systolic contraction and expelling it due to the elastic recoil of these arteries pushing blood forward during diastolic relaxation of the cardiac cycle ²⁹.

Once the LV contracts, oxygenated blood in the systemic circuit is carried throughout the body via blood vessels known as arteries via a pressure gradient ³⁰. Arteries carry blood away from the heart, eventually branching into smaller vessels known as arterioles ²⁹. Upon further progression, arterioles will branch into even smaller vessels known as capillaries, where nutrients and wastes are exchanged ²⁹. These capillaries combine with vessels known as venules, designed to carry blood to a vein for blood to be returned to the heart for the process to repeat. The blood that will travel back to the heart via the pulmonary circuit has less oxygen due to much of the oxygen going to cells throughout the body during systemic circulation ²⁹. Blood in the pulmonary circulation will go to the lungs for gas exchange and thus the cardiac cycle will begin again ²⁹.

Upon contraction of the LV, the forward pressure wave generated is propagated along the arterial tree at a relatively slow rate ²⁹. As the wave travels distally and encounters regions of diameter mismatches, it will amplify the forward traveling wave and produce a partial wave reflection. Within the arterial tree in a healthy, young, individual the amplified forward wave will lose the pulsatile force as it travels deeper into the vasculature, before hitting the microcirculation. Also, the reflected waves summate and return back to the heart during diastolic filling, just when the aortic valve is closing, helping to perfuse the myocardial microvasculature ². This allows for minimal pressure to be endured by the LV during systolic contraction and as a mean for increasing pressure during diastole. Indeed, the heart and vascular tree are efficient in young, healthy, individuals validating the claim by A.V. Hill that the amount of energy the heart has to produce and endure with each cardiac cycle with other things being equal is the elasticity of the arterial system ³¹.

2.1.2. Normal Endothelial Function

Arteries transport blood throughout the body and are composed of three layers: tunica intima, tunica media, and tunica adventitia. The tunica intima is the innermost layer and consists of a layer of endothelial cells, which are in direct contact with blood flow ^{17,29}. The tunica media is the middle layer and consists of smooth muscle and elastic fibers arranged in a circle-like pattern. This layer is thicker in arteries than in veins so that it can withstand higher pressure loads as blood is ejected from the heart. Smooth muscle is present in this layer and is supported by connective tissue consisting of elastic fibers. This layer can contract or relax to modulate

blood pressure, thus decreasing or increasing the lumen diameter, respectively. With smooth muscle contraction in the tunica media, vasoconstriction occurs and blood flow decreases, which increases blood pressure due to an increase in resistance. On the contrast, vasodilation increases blood flow due to smooth muscle relaxation and an increased lumen diameter, thus causing a decrease in blood pressure. The outermost layer, known as the tunica adventitia, is primarily made up of collagen and elastic fibers.

Arteries that are closest to the heart have extremely thick walls which contain a large amount of elastic fibers in all three tunics. These types of arteries are known as elastic arteries and the high amount of elastic fibers are needed to allow blood pumped from the ventricles to pass through them and recoil after the blood surge has passed. If the artery walls had more collagen rather than elastin present in them, they would be more rigid and unable to expand and recoil as well, causing resistance to blood flow to increase, thus increasing blood pressure due to the workload of the heart having to increase. Unfortunately, with vascular aging brings about the elastin depletion and collagen formation^{20,32,33}. While arteries naturally stiffen due to biological aging, they can also stiffen due to the manifestation of many cardiovascular risk factors, such as hypertension, obesity, hyperlipidemia, and hypercholesterolemia³⁴. Both functional and structural changes can occur that play a role in arterial stiffness, due to actions and interactions between cellular/molecular mechanisms.

Figure 1.2: An illustration depicting the three layers of an artery.

These three layers play a major role in vessel stiffness and can change with different conditions. With functional changes, changes in the vessel are related to the changes in endothelial functioning, such as during the response to stress, while structural changes are associated with changes in the levels of elastin and collagen. Elastin is an elastic protein in connective tissue that returns to its' original shape after stretching or contracting, allowing greater compliance of vessels. Collagen is a rigid protein that helps makes up the walls of arteries in the body, which helps to give the vessels their strength and structure. The more collagen there is, the stiffer and less compliant vessels become ³⁵.

With functional changes, typically nitric oxide (NO), a powerful vasodilator is reduced. NO within the endothelium helps modulate arterial tone during different conditions, such as with

exercise induced shear stress ^{25,36}. The endothelial-dependent response to vasodilate is largely due in response to shear stress by a release of NO synthesized from the combination of the amino acid L-arginine with endothelial nitric oxide synthase (eNOS) ^{25,36}. The newly created NO will bind to NO receptors of the basal lamina, leading to the production of intracellular cyclic GMP, which will cause vasodilation via inducing smooth muscle dilation ^{25,37}.

Shear stress is the mechanical force of blood flow on the endothelial cells of the blood vessel. Endothelial cells within the vasculature line the inner walls of blood vessels and are directly exposed to blood flow ³⁸. If a large enough pressure force is detected within the vessel, mechanoreceptors are activated within the vascular smooth muscle cells and an enzyme known as eNOS is activated. L-Arginine, an amino acid found in the body, gets converted to nitric oxide with the presence of eNOS, thus promoting vasodilation. NO helps suppress vascular smooth muscle cell contraction, limiting of clotting and adhesion of platelets and monocytes that contribute to atherosclerosis and eventually, arterial remodeling ³⁹.

2.1.3. Cardiovascular Dysfunction

As one ages or becomes diseased, the cardiovascular system begins to become impaired and not function as efficiently. With aortic aging and stiffening, aortic pulse wave velocity (PWV), which is how fast the pressure waves within the vasculature travel, begin to increase ²⁹.

Arteries stiffen with age due to elastin splitting and fragmentation which causes the transfer of stress to be applied to a more rigid protein known as collagen ^{3,20,33}. This is due to the repetitive strain with each cardiac cycle and in all nonliving materials (e.g. elastin), which are not

continuously replaced, fatigue and fracture take its toll. While changes are more pronounced in large, elastic arteries like the proximal aorta as compared to peripheral, muscular arteries like the brachial artery, fatigue and the consequences of strain are due to the number of stretch cycles with each beat of the heart ³. An example of this phenomenon occurs with rubber; as natural rubber undergoes a repetitive stretch of 10% (similar to that of the proximal aorta), the rubber will break after 1 billion cycles, which represents 30 years of aging in humans at a heart rate of 70 beats/min ²⁹. As a model for peripheral muscular arteries, the rubber underwent a 3% stretch cycle and was found to break after more than 3 billion cycles, representing a full lifespan of an individual ²⁹. Therefore, arterial stiffening leading to cardiovascular dysfunction is the story of what happens to an individual after 30 years of age.

Figure 1.3: An illustration demonstrating the propagation of the incident wave (Pi) along the arterial tree and upon reaching a bifurcation, a reflected wave (Pr) traveling back towards the heart. From Ref 71.

The aorta undergoes stiffening and dilation with age, leading to an increase in pulse pressure (systolic blood pressure-diastolic blood pressure) ^{2,29,40}. While aging causes dilation of proximal elastic arteries, conduit function of the arterial tree is not disrupted. However, the dilation and increased pulse pressure have a detrimental effect on the cushioning function of the arterial system, exposing vulnerable organs such as the brain, kidney, and heart, to severe consequences ². While the increased pulse pressure is due to stiffening of the elastic arteries, another prominent factor is the increase in pressure after the proximal aorta due to early wave reflection ^{3,29,40}. Increased arterial stiffening due to aging consequently causes an increase in PWV ^{29,41}, leading to early wave reflection.

While aortic stiffening leads to an increase in pressure during systole, it also causes a decrease in pressure during diastole due to the reflected wave arriving during early systole instead of late systole/early diastole ^{17,29,40}. An increase in systolic pressure causes the LV to work harder (afterload), leading to LV hypertrophy and an exacerbated oxygen requirement of the LV ⁴². Due to the increase in oxygen requirement, this predisposes the hypertrophied heart to ventricular heart failure due to prolonged contraction and slower relaxation at any given heart rate ²⁹. With the reflected wave arriving prematurely and systole lengthened and diastole shortened, perfusion of the coronary arteries are minimized, increasing the risk of myocardial ischemia ². This is caused by decreased aortic filling pressure during diastole, reduced period of diastole and lengthened duration of ejection duration, due to LV hypertrophy.

Figure 1.4: Flow chart summary of age induced vascular stiffening consequences. From Ref 2.

Arterial stiffness also increases stress on weakening arteries and predisposes vessels to increased risks of atherosclerosis, plaque rupture, stroke, and renal malfunction ^{2,14}. This is due to the failure of cushioning pulsations in proximal arteries and allowing those pulsations to propagate deeper into the microcirculation, which is comprised of smaller, resistance vessels that act as conduit vessels rather than cushioning vessels and lead into the capillaries ². As a consequence of this, damage can occur deep into the delicate microvasculature due to endothelial cell shedding or medial muscular stretching and rupture ⁴³. If pulsations are not absorbed in the proximal elastic arteries, they will most likely be absorbed in the brain and kidneys as the vessels leading to these organs are more dilated than elsewhere and would allow the pulses to transmit down easier. It is here in the microcirculation of the brain and kidney that harsh lesions are found in older individuals ^{44,45}. It is imperative that interventions to

reduce arterial stiffness and early wave reflections are studied extensively to help prevent, delay, or improve cerebral and renal dysfunction in older individuals ⁴⁶.

2.1.4. Vascular Dysfunction

Generally, the aging process expedites vessel wall stiffening in both peripheral muscular arteries and large elastic arteries, with a greater effect on the latter. There is a 70% increase in aortic stiffness and a 20% increase in peripheral stiffness when comparing early to mid-life (10-50 years old) ²⁹. This is due to large elastic arteries having a higher elastin to collagen ratio compared to peripheral arteries where collagen predominates. Large elastic arteries must be more distensible to store the ejected blood from the heart and recoil to propel the blood down the aorta. As such, large elastic arteries need to withstand higher pressure loads during distension due to their proximal location near the heart while the peripheral arteries do not.

Interestingly, despite the large elastic arteries becoming stiffer with aging or hypertension, it appears that the peripheral muscular arteries do not become stiffer ^{47,48}. It is known that arterial stiffness is non-uniform in its development and will vary throughout the systemic circulation ⁴⁹. The development of arterial stiffness has multiple mechanisms involving structural and functional changes to an artery. Structural changes are typically related to changes in the ratio of collagen and elastin, while functional changes correspond to function changes of the endothelial.

Vascular Remodeling

Structural changes to an artery are associated with changes in the levels of elastin and collagen. As mentioned earlier, elastin is a protein that allows greater compliancy of blood vessels. The elasticity of an arterial segment is not constant, but rather fluctuates depending on the amount of pressure being exerted with higher pressures recruiting more collagen fibers and decreasing elasticity⁵⁰. Likewise, collagen being a more rigid protein, if elevated, will lead to stiffer and less compliant vessels^{17,29}. Collagen is degraded slowly and is cross linked by advanced glycation end products, that are not only higher in stiffened arteries, but also helps to increase stiffness even further⁵¹. These changes cause thickening and structure remodeling within all three layers of the artery⁵².

Functionally, with aging and the development of atherosclerosis, endothelial cells secrete less vascular protective substances and more pro-atherosclerotic substances¹. With endothelial cells secreting more pro-atherosclerotic substances rather than vascular protective substances, this creates a condition known as endothelial dysfunction. Studies have shown that with the development of a stiffer vessel wall, this may contribute to a decline in eNOS production, which would further increase vascular stiffness¹. This dysfunction is associated with decreased nitric oxide bioavailability and a decreased ability to augment artery wall diameter, leading to an increased pressure in the vessel and possibly increased risk of damage in the walls of the artery. With less nitric oxide bioavailability, arterial tone is not modulated as well and as observed with aging, the pulse pressure wave will travel down the aorta at a faster rate and with a greater

proportion of the wave traveling into the microcirculation. This dysfunction over a period of time can lead to changes in the structural composition of the arteries, due to structural damage, which can further exacerbate functional changes, all playing a role in the development of arterial stiffness⁵³. A cycle is thought to exist where stiffening leads to endothelial imbalance, which may worsen stiffening¹⁷.

2.1.5. Endothelial Function Measurements

PWV is a measure of arterial stiffness, or the rate at which pressure waves travel along arterial segments, typically the carotid and femoral artery sites. PWV is known as the gold standard for measuring arterial stiffness and has been associated with cardiovascular mortality⁵⁴. Aortic stiffness is an independent predictor of CVD^{55–58}. In patients with essential hypertension⁵⁴, end stage renal disease^{59,60} and impaired glucose tolerance and diabetes mellitus⁶¹, arterial stiffness has been shown to predict coronary artery disease^{62–65}.

For a given heart rate, the time of arrival of the reflected wave depends on the PWV, which is determined by the stiffness throughout the arterial tree. The stiffer the vasculature, the faster the arrival of the reflected wave. PWV is calculated by measuring the foot-to-foot waveforms between the carotid and femoral sites and determining the delay between the appearances of each waveform, known as Δt . The measurement of the tonometry transit distance is recorded by measuring the carotid pulse site with the suprasternal notch and then the suprasternal notch with the femoral pulse site by using a measuring tape. The aortic transit distance is

estimated by subtracting two times the suprasternal notch-carotid distance from the tonometry transit distance ⁶⁶. Aortic PWV is then estimated by dividing aortic transit distance by Δt , using a validated computerized system ⁶⁶⁻⁶⁸.

Figure 1.5: Pulse wave velocity illustration and waveform analysis (Ramachandran Vasan, 2008).

While PWV is the gold standard for measuring arterial stiffness, it is important to note reference values that can be applied to norms within the population. There is a significant increase in cardiovascular risk when aortic PWV is > 11.8 m/s compared with slower values of 7.7 m/s or below ⁶⁹. A decrease in PWV of 1 m/s decreases the risk of cardiovascular disease by 15% ⁷⁰.

While reference values have been reported for PWA ^{71,72}, only one study has been able to determine reference values ⁷².

PWA over the years has gained considerable attention as a means of measuring central blood pressure, the pressure in the aorta located near the heart. Measuring central blood pressure via PWA has been shown to be a better clinical measure of blood pressure compared to the traditional brachial blood pressure measurement due to variations of blood pressure throughout the arterial tree ⁷³. Central blood pressure has shown to be more sensitive than peripheral blood pressure with the use of pharmacological interventions ⁷³. Central blood pressure has been proven to be a better indicator of future cardiovascular events compared to brachial blood pressure ⁷⁴. This is due to only the central blood pressure, not the brachial blood pressure, directly affecting target organs due to their proximity within the aortic tree ⁷³. The brachial blood pressure amplitude may be 50% greater when compared to central blood pressure values in young individuals, whereas in older individuals, central and brachial blood pressures are nearly equal ⁷³.

When the forward wave travels from the left ventricle and reaches the periphery, it encounters vessels of greater impedance that act as a mirror and reflect subsequent waves back to the heart. The wave reflection leads to augmentation of the aortic forward pressure wave due to the incident wave and the reflected wave summing together. Augmentation pressure measures how the reflected wave impacts systolic blood pressure, either by increasing the

pressure the heart must contract against or by increasing the filling pressure of the ventricles.

This augmented pressure represents wasted left ventricular energy, or, the extra workload the ventricle must generate during the reflected wave duration. This is wasted energy because there is no boost to blood flow during this time period ⁷⁵ and as mentioned earlier, is associated with LV hypertrophy and heart failure.

Augmentation index is looking at the effect of the reflected wave reflection on the second systolic peak, thus allowing one to see the additional workload the left ventricle must overcome during a cardiac cycle. Since augmentation index is relative to pulse pressure, it is often standardized to a specific heart rate of 75 beats per minute ⁷⁵. This is used as a measure to evaluate arterial stiffness. With changes in heart rate causes an inverse relationship with augmentation index. A faster heart rate decreases the ejection duration of the heart, which causes the reflected waves to arrive earlier. With faster heart rates, the reflected wave is more likely to return during diastole, decreasing the workload of the left ventricle and increasing the perfusion of the coronary arteries.

PWA is possible through applanation tonometry, which consists of pressing an artery of interest, in this case the radial artery, against a bone and recording the pressure waveforms.

Once 10 similar waveforms are recorded, a new pressure waveform is created, representing the aortic pulse wave. The pulse pressure waveform is formed from the combination of the incident wave (pressure wave generated from the left ventricle) and the reflected waves back from the

periphery, due to arterial tree branching and arterial vessel diameter changes. The pulse pressure waveform varies in different vessels and is dependent on four things: elasticity of the arteries (wave amplification is increased going from elastic areas to stiff areas), viscosity of the blood, wave reflection, and wave dispersion. Thanks to the general transfer function, which is a mathematical equation in computer software, by measuring peripheral waveforms, a central waveform can be calculated and displayed digitally.

2.1.6. Exercise for Vascular Dysfunction

Endothelial dysfunction is the cause of nearly all lifestyle related vascular diseases with the intima within the endothelium being responsible for vascular homeostasis by regulating arterial dilation and constriction. One prominent feature of intact endothelial function is NO production via eNOS formation and release. With NO serving multiple roles ranging from anti-inflammation to platelet adhesion inhibition to dilation, one thing is clear that NO is essential for vascular homeostasis ³⁹. It has been shown that impaired NO bioavailability has an independent prognostic value for adverse cardiovascular events in individuals who have risk factors, but no diagnosed coronary artery disease or coronary atherosclerosis ⁷⁶. In addition, it has been found that those present with endothelial dysfunction are at a 3-4 fold higher risk for myocardial infarction or ischemic stroke compared to those with intact endothelial function ⁷⁶.

Exercise has shown to increase expression and release of eNOS in humans due to increased levels of shear stress ⁷⁷. This is due to the increase of blood pressure with exercise stretching

out the walls within the endothelium and as a compensatory mechanism, NO is released to allow the vessel to expand, normalizing the amount of pressure exerted against the vessel wall³⁷. With repeated episodic increases in shear stress due to exercise, vascular adaptation and remodeling begin to occur. Arteries increase in size, or dilate, causing shear stress to be normalized within the body, a phenomena known as “athlete’s artery”, defined by large lumen with a thin wall and normal endothelial function³⁶. However, the degree of change within the vasculature is not clear, with results dependent upon not only an individual’s health and fitness level, but also the exercise intensity³⁶.

Exercise intensity, duration, and frequency all play a role in the total volume of exercise achieved weekly. While each of these factors are important, it appears that the total volume of exercise is most important in observing reductions in CVD or functional capacity⁷⁸. With time being the number one barrier for exercise adherence, exercise regimes that offer the most enjoyment along with results are heavily warranted. HIIT and MICT have undergone a plethora of studies comparing the two in hopes of finding the optimal exercise prescription for reducing CV risk and mortality and increasing functional capacity in the general population.

2.1.7. HIIT versus MICT

HIIT was originally developed for athletes who were already highly trained, as it appears that additional increases in submaximal endurance training did not appear to further enhance performance or $\text{VO}_2 \text{ max}$ ⁷⁹. At the time it seemed that further increases in performance was only possible through the implementation of HIIT⁸⁰. While recreational exercise and endurance

training stimulates physiological responses due to increased muscle cell energy demands, it is generally believed that in sedentary and recreationally active individuals, several years of training are needed to improve VO_2 max to that of highly trained athletes ⁷⁹. However, this was disproven as one study utilizing a HIIT intervention showed that several subjects who were recreationally active/sedentary improved their VO_2 max to that of highly trained athletes (VO_2 max > 60 ml/kg/min) ⁸¹.

The rationale for HIIT is that exercise is performed at a greater workload than one can typically endure for a continuous period, but by incorporating periods of rest known as “active recovery”, workloads of high intensity can be completed in brief intervals allowing for supraphysiological benefits. While high lactate levels develop during the intervals, the active recovery allow the opportunity for lactate to be partially removed from the body, allowing one to tolerate the repeated intense intervals for extended periods of time ⁸². It has been reviewed and stated that HIIT is a more potent stimulus for improving vascular endothelial functioning comparing to MICT, even after one single exercise session in adolescents and adults with risk factors for vascular dysfunction ⁸³. These changes to the cardiovascular system state an improvement in oxygen delivery to working muscles and to an increase in stroke volume ⁷⁹. By increasing stroke volume, the LV contracts with a greater force via an increase in cardiac filling during diastole, improving end-diastolic volume and consequently, producing a more forceful contraction via the Frank Starling Mechanism in the next cardiac cycle ²⁹.

It is also important to note that MICT is also beneficial as an independent exercise regime. Indeed, MICT has been found to tax the aerobic system in an individual and as a result, peripheral and central adaptations have occurred. Central adaptations including the improved rate of oxygen delivered to working skeletal muscle fibers in combination with increased utilization of oxygen in the periphery of working muscles⁸⁴. Endurance training has also been found to lower resting heart rate and increase blood and plasma volume, allowing for improvements in stroke volume and perfusion throughout the body⁸⁵. Interestingly, while these central improvements allow for increases in physical work capacity, longer, more strenuous training regimes may be needed for improvements in VO_2 max⁸⁶. It is speculated that with this style of exercise training, several weeks may be required before observable changes in muscle capillaries and mitochondrial density take place⁸⁷. Additionally, peripheral adaptations resulting in reductions of glucose levels and improvements in glycogen utilization⁸⁸ have been found with endurance training, as well as more efficient blood lactate maintenance during absolute workloads⁸⁹ with an endurance training exercise intervention. It has also been suggested that mitochondrial density, enzymatic activity, anti-inflammatory cytokines, and skeletal muscle adaptations is improved in both MICT and HIIT exercise interventions, with a greater effect on the latter^{8,79,90,91}.

When comparing HIIT and MICT for body composition, the results are not so clear. In 2014, one-third of the population was considered overweight while 13% were considered obese⁹². While exercise has been proven to be an effective intervention for preventing weight gain and losing weight, when looking at overweight and obese individuals, it appears that exercise alone

is not effective in weight loss without dietary interventions when evaluating only BMI or body mass ⁹³. While one would speculate that HIIT is very intense exercise, it should burn more calories over a period when matched with frequency to MICT, however, HIIT has more complex outcomes.

In an ideal exercise prescription for weight loss, the program design should be feasible and enticing for patients and eventually, adopted as a lifestyle behavior. Surprisingly, HIIT may induce a compensation with food intake. By exercising extremely hard, subjects feel exhausted and as a reward, consume more calories than they burn, however, this is not supported with some studies ⁹⁴. Recently, a review was published examining the effects of HIIT and MICT on body composition in overweight/obese individuals and the results show that these two exercise prescriptions induce similar modest effectiveness in body composition changes independent of body-weight changes ⁹⁵. In this review, HIIT and MICT also showed similar adherence rates, despite HIIT having ~40% less time commitment than MICT. It should be noted however, that there is no evidence of body composition changes in healthy, older individuals when comparing MICT to HIIT ⁹⁶. Finally, it was found that the measurable changes in body composition were heavily influenced by the exercise modality, with treadmill running showing significant decreases in body mass and fat mass compared to cycling, which showed no significant changes in body composition ⁹⁷. While the underlying mechanisms are not clear on why this may be, perhaps the increased muscle mass recruitment needed for running at any given workload leads to greater energy expenditure compared to cycling ⁹⁸.

2.2. Arterial Stiffness

CVD is the leading cause of mortality in the world with over 600,000 deaths annually ¹². In the United States, 11.3% of the population, approximately 26.6 million individuals, suffer from CVD ⁹⁹. As such, vascular physiology has been studied heavily in hopes of determining the influence of vascular pathophysiology on CVD related events, such as heart attacks and strokes. One area of research that has been linked to systolic hypertension ¹³, coronary artery disease ¹⁴, stroke ¹⁴, and heart failure ¹⁰⁰ looks at stiffening of the central arterial tree (aortic tree), known as arterial stiffness. Arterial stiffness results in a gradual loss of elasticity of the arteries, leading to an increase in blood pressure within the vessels, thus increasing CVD risks and mortality ⁷⁰.

2.2.1. Aging

Aging causes a cascade of changes in the cardiovascular system that are both modifiable and unavoidable. One of the most consistent changes is dilation and hardening of the large elastic arteries. As mentioned earlier, while large elastic arteries are more vulnerable to age related stiffening and cannot be prevented, interventions that can delay the progression of stiffness in these vessels and muscular peripheral arteries are paramount. This is especially important as the number of subjects in the United States aged 65 years and older are growing at a rate faster than that of the total population ¹⁰¹.

There is a curvilinear relationship with age and aortic PWV with evidence showing PWV to be less pronounced in younger individuals as compared to older adults beyond the age of 50 ¹⁰².

Between ages 20-30, PWV is estimated to increase by 0.4 m/s, but after age 50, there is an accelerated increase in PWV, which has been shown to increase ~1.8 m/s between 70-80 years of age ¹⁰². There is evidence showing that when traditional cardiovascular risk factors are controlled for, including blood pressure, an increase in aortic PWV by 5 m/s constitutes 10 years of vascular aging ⁵⁴. Although most attribute increases in life expectancy as a positive advancement in science and medicine, unfortunately, a longer life expectancy does not necessarily represent better health conditions. By pushing life expectancy further and further, this also increases the occurrence of chronic diseases for a longer period. This can be due to a longer time period living with a chronic disease, be it from earlier diagnosis and/or improved healthcare ¹⁰³. As such, this can allow for the manifestation of CVD, eventually leading to or accelerating the process of cardiovascular and endothelial dysfunction.

2.2.2. Hypertension

Blood pressure is a traditional measure that is easily measured using a sphygmomanometer to help determine the risk for future cardiovascular events. Advancing age causes increases in systolic blood pressure while diastolic blood pressure remains the same or decreases slightly, which leads to a widening in pulse pressure ¹⁰⁴. Systolic hypertension is extremely close to aging, so much that people aged 65 years and older have a 90% chance of developing hypertension in their lifespan ³³. Due to increases in arterial stiffness and pressure wave augmentations, isolated systolic hypertension is the most common subtype of hypertension for individuals middle aged and older ¹⁰⁴.

The most common form of “classical” essential hypertension that affects young and middle-aged individuals is mixed hypertension (systolic/diastolic). This abnormality in blood pressure regulation has been identified to the increase in peripheral vascular resistance. While there is a consensus that muscular artery stiffness is increased in hypertensive subjects due to higher operating pressures, interestingly, muscular arteries show dilation in hypertensive subjects ¹⁰². This causes a paradoxical increase in vessel compliance, although, increased wave reflection ¹⁰⁵ and augmentation index ²⁹ have also been shown in the same subjects. This leads to the conclusion that vessel wall remodeling due to hypertension is likely a compensatory mechanism in response to vessel wall stress ¹⁷.

Large elastic arteries have also shown increased stiffness due to hypertension, as made evident by increases in aortic PWV compared to normotensive subjects across a wide age range ^{106,107}. It is unclear, however, if increased aortic stiffness is due to the higher operating pressure of the hypertensive arteries. It has been found that in young, hypertensive subjects, arterial stiffness levels are similar to that in older, non-hypertensive individuals ¹⁰⁸. The same study also found that when blood pressure is decreased in young, hypertensive subjects, arterial stiffness levels decrease, suggesting that blood pressure does influence arterial stiffening early on in life ¹⁰⁸. While blood pressure influences on arterial stiffness is complex and difficult to pinpoint, it appears that blood pressure and arterial stiffness go hand in hand, creating a feedback loop and increasing/decreasing expression of one another ⁴⁹.

2.2.3. Diabetes

Physical inactivity is known to cause an increase in developing type 2 diabetes globally ¹⁰⁹. In the United States, only 28.2% of diabetic patients achieve the recommended level of physical activity ¹¹⁰. It is known that diabetes causes an abnormal metabolic state that can help lead into arterial dysfunction and CVD. Indeed, adults with diabetes are 2-4 more times likely to develop heart disease or stroke compared to adults without diabetes ¹¹¹. Two major features of diabetes are hyperglycemia and insulin resistance.

Hyperglycemia is a major risk factor for microvascular complications with its pro-atherosclerotic environment ¹¹². Insulin resistance is an abnormality in type 2 diabetes that brings about a clustering of metabolic disorders such as obesity, hypertension, and dyslipidemia, each representing an independent CVD risk factor. Both of these conditions have been associated with large elastic artery stiffness ¹¹². This is due to diabetes causing an increase in collagen cross linking and endothelial dysfunction. With stiffening of these arteries, the buffering abilities and elastin to collagen ratio is decreased, leading to increases in pulse wave propagation speeds. It has been noted that those with diabetes experience an acceleration in arterial aging and an increase in pulse pressure at earlier ages compared with nondiabetic individuals ¹¹³.

Obesity has also been linked to the pathophysiology of diabetes via insulin resistance. Visceral adipose tissue presents elevated free fatty acids within the circulation that contributes to insulin resistance ¹¹⁴. It is also known that increased levels of adipose tissue lead to the release of pro-inflammatory cytokines, which can have negative consequences on the vasculature by

inducing a state of chronic, low-grade inflammation, helping to contribute to atherosclerosis and future CVD risk ¹¹⁴.

2.2.4. Body Composition

The accumulation of excessive body fat, known as obesity, is a rapidly increasing, significant health concern. Since 1980, those considered overweight (body mass index [BMI] $>25 \text{ kg}^{-2}$) and obese (BMI $>30 \text{ kg}^{-2}$) has doubled globally ⁹². Over 39% of adults were considered overweight with an additional 13% labelled as obese in 2014 ⁹². Obesity is a major risk factor for the development of chronic conditions such as CVD and metabolic diseases, which can lead to atherosclerosis, type 2 diabetes, and all-cause mortality ¹¹⁵.

Increased levels of adipose tissue have been linked with increases in arterial stiffness throughout the life cycle ⁴⁹. Adolescents who are overweight and obese exhibit higher aortic and brachial SBP and pulse pressure compared to normal weight counterparts ¹¹⁶. Aortic PWV has also been shown to be 7% higher in overweight/obese individuals ¹¹⁶. One study found that when adults of normal weight were fed a caloric surplus of 1000 kcals per day across 6-8 weeks, total abdominal fat, visceral fat, and waist circumference increased in a linear fashion with arterial stiffness by 13% ¹¹⁷. Another study found that childhood obesity was associated increases in large elastic artery stiffness into adulthood ¹¹⁸.

The benefits of physical activity on weight management has been made evident in a plethora of studies. While exercise has a mild effect on reducing total body weight, caloric restriction has

shown much stronger results on weight management, but not in reducing visceral adipose tissue ¹¹⁹. Both are recommended for the best results, as weight loss is associated with a reduction in aortic stiffness ¹²⁰. This study found that after one year of lifestyle intervention implementing both exercise and caloric restriction, aortic PWV decreased by 0.581 m/s after 6 months and 0.32 m/s after one year ¹²⁰. Typically, endurance-based exercise programs were used for weight loss due to longer duration sessions, however HIIT has grown more popular as a shorter alternative method of exercise that offers similar/greater results to that of MICT programs. To this day, there is still no consensus on what the appropriate modality for exercise should be for improvements in body composition

2.2.5. Physical Inactivity

Physical inactivity is a modifiable cardiovascular risk factor that costs \$53.8 billion in healthcare costs globally ¹²¹. Physical inactivity and a sedentary lifestyle has been shown to be associated with increased levels of arterial stiffness ⁴⁹. While aging is the strongest predictor of arterial stiffness for both men and women, chronic, regular exercise can blunt age-related arterial stiffness level increases. This was made evident in a study that looked at physically active post-menopausal women aortic PWV compared to pre-menopausal women with similar aortic PWV ¹²². Unfortunately, a significant difference in PWV was still seen between the two groups, implying that regular levels of physical activity cannot completely reverse the age-related increases in levels of arterial stiffness.

Higher levels of CRF have been shown in both males and females to be associated with a decrease in PWV through reductions in resting heart rate ¹²³ and adipose tissue levels ¹²⁴, respectively. Reasons for this being is that with a lower heart rate, the cardiac cycle duration is prolonged, which will delay the forward wave and cause the reflected wave to arrive back during late systole/early diastole. Mechanistically speaking, this is likely due to several factors, with the first being an increase in shear stress. As mentioned earlier, shear stress is the mechanical force of blood flow exerted on the innermost layer of blood vessels known as the intima. With increased levels of shear stress, NO is created more readily due to increased eNOS activation and release, thus increasing NO bioavailability, and inducing smooth muscle relaxation. This causes stress transfers from collagen fibers to elastic fibers, thus slowing down the velocity of wave propagation and reflection.

A second factor would be a decrease in vasoconstrictors (e.g. endothelin-1). Vasoconstrictors make the vessel stiffer by reducing the lumen diameter, making peripheral resistance increase, consequently increasing blood pressure. This would allow for platelet adhesion, coagulation, and inflammation to occur more easily, increasing the long term risk of atherosclerosis ²⁵. By decreasing vasoconstrictor release, vascular tone can be decreased and help keep the endothelium in a state of vascular homeostasis. Unfortunately, the best mode of exercise is not known, with mixed reviews regarding MICT and HIIT ²⁷.

Chapter 3

Methods

3.1. Experimental Design

The purpose of this study was to examine the effects of an 8-week aerobic exercise program on arterial stiffness in healthy, sedentary individuals and to determine the effects on arterial and cardiac adaptations, as well as any change in exercise performance. This interventional study included 4 groups; a control group and 3 exercise training groups. All subjects were between the ages of 18-40 years old, free of any cardiovascular, pulmonary, or metabolic diseases and were not participating in an exercise training program greater than 3 days per week. Each subject arrived at the Human Performance Lab located (HPL) at the Health Sciences Center at West Virginia University to undergo two evaluation sessions, before and after the 8-week intervention. Subjects arrived at the lab after an overnight fast, withholding caffeine and medications the morning of the tests. All evaluation sessions took place in the morning between 5:00 and 10 AM to avoid circadian rhythm bias. After 15 minutes of quiet supine rest, subjects underwent supine measures of arterial structure/function.

Height and weight, along with waist and hip circumference were measured using standard lab procedures. Fat distribution was measured in a standing position via waist circumference at the smallest circumference location between the rib cage and iliac crest. Hip circumference was measured at the largest circumference location between waist and thighs. Body composition was assessed from body volume via the BodPod (Life measurement, Concord, CA, USA). Subjects wore tight fitting bathing suits and a swim cap during the measurements in the BodPod. BMI was calculated as $\text{weight (kg)}/\text{height (m)}^2$.

Subjects performed an incremental exercise test on a cycle ergometer, using a customized YMCA bike test that increased by 25 watts every 3 minutes. Subjects were instructed to maintain a cadence of 50 revolutions per minute throughout the entire test. The ergometer was placed at a 45-degree angle during the stress test. A cycle ergometer was used as the stress test modality of choice due to our lab finding significance results with exercise interventions in the past using this modality. The cycle ergometer also may provide a sense of safety to subjects with maximal exertion, as well as feelings of more overall comfortableness. Expired gases were collected using a one-way valve and analyzed using a metabolic cart (ParvoMedics TrueOne 2400). HR was recorded throughout each 3-minute stage using a 3-lead ECG. BP was measured by an experienced investigator using a manual sphygmomanometer at rest, halfway of each stage, and at 1, 3, and 5 minutes of recovery. Exercise was terminated for any of the following reasons: SBP rose above 250mmHg, the subject requested to stop, any significant arrhythmias' developed, or if the subject was unable to maintain a cadence of 50 revolutions per minute.

Initial exercise training was performed at the HPL. The exercise sessions were either 25, 40, or 47 minutes at 70% and/or 90% Heart rate reserve (HRR), depending on the exercise group placed into, for 3 sessions per week for 8 weeks. These particular time durations and intensities were chosen based off of popular protocols done within the literature for various populations. The 40 minute exercise protocol is the most popular version of HIIT that has been heavily studied in the average population and originally was compared to 47 minutes of moderate intensity exercise in metabolic syndrome patients ¹²⁵. The 25 minute LV-HIIT protocol ⁹¹ was originally developed to examine the efficacy on type 2 diabetic patients who were

overweight/obese. Positive metabolic health parameters were concluded and with time being the number one limitation for lack of exercise, it seemed fitting to explore this shortened version of HIIT.

Each subject had the choice to exercise on either a bicycle, treadmill, or elliptical every session, depending on their preference. Subjects individually exercised at 70% HRR if placed into the CT group (47 minutes) and/or 90% HRR if placed into a HIIT group (25 and 40 minutes). The appropriate heart rate zones were calculated based off the resting HR obtained during PWA measurement and maximal HR was obtained during the maximal stress test. Exercise intensities were based on HRR calculations rather than age-predicted maximal HR to more accurately fit each individual, as this formula takes into account both maximal heart rate and resting heart rate of each individual. Adherence to the exercise prescription was documented through the use of self-reported physical activity logs. All post-test measurements were performed at least 48 hours following the last training session. Subjects who were placed into the control group were asked to maintain their normal daily lifestyle and activity level.

3.2. Training Protocol

Subjects placed into the CT group exercised for 47 minutes, 3x/week for 8 weeks at 70% HRR. Subjects placed into the LV-HIIT group exercised 25 minutes, 3x/week for 8 weeks at 70% and 90% HRR. In this group, there was a 3-minute warm up at 70% HRR, followed by a 1-minute 90% HRR interval interspersed with 75 seconds of active recovery at 70% HRR. Subjects did this

for a total of 10 rounds. Subjects placed into the HIIT group exercised for 40 minutes, 3x/week for 8 weeks at 70% and 90% HRR. In this group, subjects had a 10-minute warm up at 70% HRR followed by a 4-minute interval at 90% HRR, interspersed with a 3-minute active recovery at 70% HRR. Subjects completed 3 more rounds of this followed by a 5-minute cool down. During exercise, all subjects wore Polar HR monitor (Polar A300) and were instructed to keep their target heart rate within a zone of ± 6 beats.

3.3. Experimental Measures

3.3.1. Pulse Wave Velocity

PWVcf was measured via applanation tonometry from the Sphygmocor AtCor Medical device (Sydney, Australia). Blood pressure was acquired from an automated cuff (Omron Healthcare Inc.) and SBP and DBP was entered prior to PWV data acquisition after 10 minutes of quiet rest. ECG-gated waveforms were recorded over the carotid and femoral arteries during recordings. PWV is calculated by measuring the foot-to-foot waveforms between the carotid and femoral sites and determining the delay between the appearances of each waveform, known as Δt . The measurement of the tonometry transit distance is recorded by measuring the carotid pulse site with the suprasternal notch and then the suprasternal notch with the femoral pulse site by using a measuring tape (in meters (m)). The aortic transit distance is estimated by subtracting two times the suprasternal notch-carotid distance from the tonometry transit distance ⁶⁶. Aortic

PWV is then estimated by dividing aortic transit distance by Δt , using a validated computerized system⁶⁷.

3.3.2. Pulse Wave Analysis

Subjects lied down supine on an adjustable bed with the right arm extended, at heart level, on foam supports angled 90° from the torso. Recordings were made possible via applanation tonometry from a strain gauge pressure sensor (AtCor Medical Device, Sydney, Australia) placed over the radial artery. By applying pressure, the artery is flattened and pressed against bone in order to record waveform readings. Once 10 similar waveforms are recorded, a new pressure waveform is created, representing the aortic pulse wave. The pulse pressure waveform is formed from the combination of the incident wave (pressure wave generated from the left ventricle) and the reflected waves back from the periphery, due to arterial tree branching and arterial vessel diameter changes. The SBP and DBP in the radial artery were recorded via an automated cuff (Omron Healthcare Inc.) and entered into the PWA software prior to data acquisition. Central SBP, DBP, and pulse pressure are determined due to the general transfer function, which is a mathematical equation in computer software, by measuring peripheral waveforms, a central waveform can be calculated and displayed digitally.

3.3.3. Carotid Intima Media Thickness

Carotid artery intima media thickness (cIMT) via B-mode ultrasonography is a useful, non-invasive tool for detecting atherosclerotic plaque presence and course of development ^{19,126}.

Indeed, cIMT measurements have been linked to be a strong predictor of future cardiovascular risk and mortality incidents ¹²⁷. This is due to the ability to examine arterial wall thickening ¹⁹, lumen enlargement ¹²⁸, and atherosclerotic plaque formation ¹²⁹ throughout the vascular, all of which play a pivotal role in various forms of CVD. Intima media thickness is measured in the space between lumen-intima and the media-adventitia structure ^{19,126}.

Using an ultrasound machine (GE vivid) equipped with a high-resolution linear array transducer, cIMT was measured 1-2 cm proximal to the carotid bifurcation. All subjects were lying supine with a slight hyperextension and rotation of the neck in the direction opposite of the probe. By placing the probe over the anterior position of the neck longitudinally, two-dimensional recordings were measured for approximately 30 seconds. cIMT was measured during diastole of the cardiac cycle by using the ECG during the end-diastolic phase, between the P and Q wave. All cIMT measurements were analyzed a total of 3 times with the average amongst the three determining the IMT value.

3.4. Statistics

All data are presented as Means $\pm$ SEM. Data from each experiment were first tested for normality using Kolmogorov-Smirnov tests. Data that were not normally distributed were analyzed using Kruskal-Wallis nonparametric tests. Normally distributed data underwent repeated measures analysis of variance for statistical significance, followed by Tukey's HSD post-hoc analysis. All analyses were performed with SPSS Statistics 25 (IBM, Armonk, NY, U.S.A.). P-values <0.05 were considered statistically significant.

Chapter 4

Results

4.1. Results

Body Anthropometry

In total, we had 40 subjects complete the 8-week exercise intervention, with 10 subjects in each group. Subject characteristics are described in table 4.1. There were no significant group differences for sex or age (Table 4.1). Hips and waist were also examined between the groups with no significant group differences reported. When comparing body composition across the 8 weeks, a significant time (pre vs post) by group interaction ($p=0.016$) was reported for total weight in the HIIT group compared amongst the other groups. The data also showed a trend for improvement in total weight in the CT group when compared amongst the groups ($p=0.084$). However, no significant changes in fat mass ($P= 0.315$) or lean mass ($P= 0.697$), was evident, respectively (Table 4.2).

Table 4.1. Baseline clinical characteristics of the study cohort

	Control (n=10)	CT (n=10)	LV-HIIT (n=10)	HIIT (n=10)
Age (years)	26±2	28±2	23±1	24±1
Height (cm)	171±3	168±3	172±3	170±3
Sex (% female)	40	80	70	60
Hip (cm)	104±2	112±4	104±3	109±5
Waist (cm)	89±3	93±5	92±3	97±6

Values are means ± SEM.

Table 4.2. Body composition changes following an 8-week aerobic exercise intervention

	Control (n=10)		CT (n=10)		LV-HIIT (n=10)		HIIT (n=10)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Weight (kg)	72±4	72±4	80±6	81±6	73±4	73±3	82±7	81±7*
Fat mass (kg)	19±3	23±5	25±4	25±4	21±1	20±2	25±4	24±5
Body Fat (%)	27±4	27±4	30±3	29±4	27±2	28±3	29±3	28±3
Lean Mass (kg)	53±4	57±4	55±4	57±5	53±3	60±9	58±5	57±4
BMI (kg/m ²)	24±1	24±1	28±2	29±2	25±1	25±1	28±2	28±2

Values are means ± SEM. *Denotes $p \leq 0.05$ compared to other groups.

Arterial function and structure

In total, we had no significant time by group interactions when comparing resting HR ($P= 0.468$), bSBP ($P= 0.979$), bDBP ($P= 0.491$), cSBP ($P= 0.812$), and cDBP ($P= 0.616$) values amongst one another in the groups, (Table 4.3). When looking at other values of central arterial function, there was no significant change for PP, cPP, or SEVR.

Table 4.3. Arterial health parameter changes following an 8-week aerobic exercise intervention

	Control (n=10)		CT (n=10)		LV-HIIT (n=10)		HIIT (n=10)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Resting HR (bpm)	65±2	68±2	65±3	66±4	67±3	66±2	61±3	60±3
bSBP (mmHg)	119±5	119±5	116±5	118±6	116±3	116±4	119±4	121±4
bDBP (mmHg)	67±4	64±3	67±3	67±3	67±3	69±2	66±2	68±3
cSBP (mmHg)	100±6	100±5	98±3	100±4	97±2	99±3	101±4	104±4
cDBP (mmHg)	67±5	65±3	67±3	67±3	68±3	69±2	66±2	68±3

Values are means ± SEM.

When examining measures of arterial stiffness, as determined via cfPWV, no significant group by time interactions ($P= 0.292$) were present across the groups (Figure 1a). Similarly, there were no significant group by time interactions in augmentation pressure found in figure 1b ($P= 0.939$). Furthermore, when examining Alx, no significant group by time interactions ($P= 0.919$) were found, as made evident in figure 1c. When augmentation was standardized to a heart rate of 75 bpm, no significant group by time interactions were present, visible below in figure 1d ($P=0.891$). Likewise, when examining arterial structure within the carotid arteries, cIMT found no significant group by time interaction ($P=0.177$) across the groups, which can be seen below in figure 2.

Figure 4.1: *Changes in arterial stiffness in response to 8 weeks of aerobic exercise across the exercise groups and non-exercise controls.* There were no changes in parameters of arterial stiffness across the intervention.

Figure 4.2: *Changes in carotid intima media thickness in response to 8 weeks of aerobic exercise across the exercise groups and non-exercise controls. There was no significant change in cIMT across the intervention.*

Exercise Capacity and Performance

When examining the effects of the 8-week exercise intervention, there was no significant changes across the groups in VO_2 peak ($P=0.761$), HR_{max} ($P=0.433$), Tidal Volume ($P=0.799$), or HR at ventilatory threshold (0.712) as seen below in figure 4.3. For further examination, we looked at group differences in Respiratory Exchange Ratio (RER) values ($P=0.085$), Rating of Perceived Exertion (RPE) values ($P=0.171$), % HR max achieved ($P=0.433$), and VO_2 peak comparing controls and subjects who underwent exercise within this study ($P=0.506$) and found no significant changes across the groups, as seen below in figure 4.4.

Figure 4.3: Changes in exercise capacity and performance in response to 8 weeks of aerobic exercise across the exercise groups and non-exercise controls. There was no significant change in panels A-D across the intervention.

Figure 4.4: Changes in maximal exercise performance values in response to 8 weeks of aerobic exercise across the exercise groups and non-exercise controls. There was no significant change in panels A-D across the intervention.

Chapter 5

General Discussion

5.1. Discussion

The present study shows that after an 8-week aerobic exercise intervention, in young, healthy adults, no changes in PWV were discovered amongst any of the groups. Only a small amount of studies have compared the effects of HIIT versus MICT on arterial stiffness using PWV ^{22,26,130}. Two studies showed that HIIT is more effective than MICT for reducing arterial stiffness in young to middle aged hypertensive patients ²⁶ and young women at an increased risk for hypertension ¹³⁰ while the other study showed that MICT is more effective than HIIT in reducing arterial stiffness in older, sedentary, disease free adults. Both studies showing that HIIT was superior than MICT in reducing arterial stiffness recruited subjects that were of similar age ranges to ours, but present with hypertension, which is known to have negative consequences on arterial stiffness levels. Indeed, PWV is less pronounced in young individuals when compared to older individuals, aged 50 and beyond ¹⁰². It is also known that between the ages of 20-30, PWV increases by 0.4 m/s ¹⁰². This may explain why we were not able to see a reduction in arterial stiffness within our study, simply because of the young age of our subjects. While we recruited sedentary individuals, our subjects were young, healthy individuals with overall, relatively low values of PWV, leaving limited room for improvement. Perhaps a higher level of baseline arterial stiffness is necessary before seeing changes in PWV values in a HIIT versus MICT intervention.

Being that arterial stiffness begins to take course beyond 30 years of age, this helps to explain why no improvement was noticed in our 8-week aerobic intervention. It is also known that the effects of exercise on measures of arterial stiffness will be more pronounced in those who

presently have cardiovascular risk factors as compared to those who are disease free ^{2,3,17,25}.

While PWV did not decrease in the HIIT group compared to the CT as we hypothesized, this reveals an important finding that in young, healthy individuals, CT and HIIT have similar effects on measurements of arterial stiffness. This allows greater variety in exercise program choices, which can be based on a variety of factors, such as intensity, frequency, and duration. While these three factors are important, it appears that the beneficial effects of exercise are heavily influenced by the volume or quantity of work performed weekly rather than intensity and duration ^{36,131}.

In our study, we found no differences in VO₂ peak between the groups. Indeed, there are a plethora of studies comparing the effects of HIIT versus MICT on VO₂ max/peak in a wide age range. It has been shown that low levels of cardiorespiratory fitness levels (VO₂ peak) are inversely correlated to increased incidence of CVD and all-cause mortality rates ⁶. In a wide variety of studies ^{27,91,132–135}, HIIT has been found to be more effective than MICT in improving CRF levels in young, middle, older, and different clinical populations. When looking at the effects of a LV-HIIT exercise regime, improvements in VO₂ max were found in a healthy, but sedentary, population with the same age range as our own undergoing a supervised 8-week exercise intervention, consisting of five exercise sessions weekly ¹³⁴. The results of the previous study are further supported with an improvement in VO₂ peak found in healthy, older adults when comparing HIIT versus MICT ¹³³. In a review comparing HIIT versus MICT in different clinical populations ²⁷, CRF levels increased significantly after a 12-week HIIT intervention compared to MICT.

While many studies show the validity of HIIT improving CRF levels to a greater extent than MICT, these findings are not universal ^{136,137}. In patients with coronary artery disease undergoing cardiac rehabilitation, subjects underwent two supervised exercise sessions per week for 12 weeks, either performing HIIT or MICT. There was no significant difference found between the two groups when examining CRF levels. In a study similar to ours, fifty-five college aged individuals underwent an 8-week aerobic exercise intervention comparing two versions of HIIT versus MICT ¹³⁷. While CRF levels improved after the 8-week intervention in both the two HIIT groups and MICT group, there were no significant differences between the groups. Regarding our study, it is difficult to explain the lack of improvement in VO₂ peak after the 8-week intervention. While we implemented exercise training logs for adherence recording and HR monitors to exercise in the appropriate intensities, this study was a non-supervised intervention, which may have influenced the results. Likewise, perhaps the 8-week intervention simply was not enough time to see statistically significant changes in VO₂ peak making it hard for our analysis of VO₂ peak to be significant (P=0.761). Maybe a 12-week intervention would have induced significant changes in VO₂ peak in our study cohort. While we did perform stress tests on a cycle ergometer for pre and post testing, it has been reported that when performing a stress test on a cycle ergometer, the recorded VO₂ max can be 7-12% lower when compared to a stress test performed on a treadmill ¹³⁸. Perhaps if we implemented a stress test protocol on a treadmill rather than a cycle ergometer, we would have seen measurable changes in VO₂ peak. Another factor is while we performed the stress testing on a cycle ergometer, subjects had the option of performing individual exercise sessions on either a bicycle, treadmill, or elliptical for every session. It has been shown that the body adapts and responds favorably to

stress testing given the specific modality of exercise training used ¹³⁹. Perhaps if subjects exercised primarily on an elliptical or treadmill, the adaptations and results did not translate significantly over to the testing modality of a cycle ergometer.

An important discovery in this study is that HIIT induced total weight loss in young, healthy individuals in 8 weeks. It has been previously reported that body composition changes do not take place in healthy, older individuals when comparing MICT to HIIT ^{96,97}. This raises potential questions to the effectiveness of HIIT in different populations and the length of the intervention. As mentioned previously, it has been reported that body weight changes from exercise are modest and relatively ineffective when compared to caloric restriction and diet intervention studies. A recent review ⁹⁷ revealed that MICT and HIIT appear to have equal effects on body composition, despite HIIT having ~40% less time commitment. The primary finding of this review is that ~10 weeks of exercise, be it HIIT or MICT, can reduce bodyfat and waist circumference in the absence of body mass changes. While we did not find a significant change in bodyfat levels or waist circumference, perhaps due a shortened intervention of only 8 weeks, we were able to find a significant decrease in total body weight from HIIT. It has been consistently reported that exercise is relatively ineffective for managing overweight/obesity without the addition of a dietary intervention ^{93,97}, but has inconsistent conclusions ¹⁴⁰. It has also been proven that exercise induces fat loss, particularly visceral fat, even if weight loss is not evident ⁹⁷, as observed in our LV-HIIT and CT groups.

While this was not a diet intervention study, finding HIIT to reduce total body weight significantly was surprising. Perhaps as the 8-week intervention progressed, subjects felt better and were happy with the results they subjectively felt, thus making small improvements in

dietary consumption. Either way, with the greatest barrier to exercise being time, evidence has suggested that HIIT is an effective modality of exercise for helping to prevent CVD to a similar degree to that of MICT, in terms of arterial stiffness, VO₂ peak, and body composition levels for those who are susceptible in withdrawing from an exercise program due to time constraints.

CVD is the leading cause of mortality in the world and a key component in the development of CVD is physical inactivity. Certain factors contribute to CVD that are unavoidable, such as aging, while there are others that can help accelerate or delay the process of CVD. Weight gain is known to impact PWV negatively, as mentioned earlier. Simply put, those who are overweight/obese exhibit greater levels of arterial stiffness measured by PWV ⁴⁹. With the reduction of total body weight in our study within the HIIT group and PWV not decreasing significantly, by maintaining healthy lifestyle habits and engaging in activities that do not promote the acceleration of arterial stiffness, this is the first approach in achieving/maintaining healthy arterial functioning and reducing the risk of CVD.

5.2. Future Directions

The results from this thesis show no change in arterial stiffness as measured from PWV amongst any of the groups. This exercise intervention recruited healthy, young, sedentary individuals who tend to have lower levels of arterial stiffness, leaving little room for improvement. As previously mentioned, arterial stiffening is the story of what happens after 30 years of age.

Interestingly, since resistance training has been shown to have detrimental effects on central arterial compliance including PWV ^{141–143}, while evidence states the opposite ¹⁴⁴, it would be

interesting to see an exercise intervention comparing the effects of HIIT versus resistance training on parameters of central arterial compliance and stiffness. We also did not employ a nutritional intervention or calorie restriction study, which has shown beneficial effects on the general population ¹⁴⁵. This would be an interesting avenue of research to compliment different types of exercise interventions on arterial stiffness levels.

Overall, our data show no differences in levels of arterial stiffness and no differences between the groups on measures of VO_2 peak. This is important as according to our data, exercise at different intensities and durations do not cause an increase in arterial stiffness after an 8-week aerobic exercise intervention. While our study reported no changes in VO_2 peak across the groups, studies have proven the validity of exercise on numerous physiological factors in 8-week interventions across age ranges and clinical populations ^{27,97,133,137}. For those who are pressed for time, the LV-HIIT is an attractive alternative for health-related benefits ^{9,91}. For those who are diseased or deconditioned and cannot handle the stress of HIIT, CT has been found to have beneficial effects as well comparable to that of HIIT. These effects, including mechanistic approaches, should be studied in comparison to resistance training on larger sized studies with a dietary intervention to further examine their efficacies on the general population and diseased population.

5.3. Limitations

The objectives of this thesis were to 1) examine the effects of an 8-week aerobic exercise intervention on arterial stiffness in healthy, sedentary adults and 2) determine the effects of an

8-week LV-HIIT aerobic exercise program compared to 8-weeks of aerobic HIIT. Unfortunately, like all other studies, this thesis contains limitations.

This study allowed for self-report bias in terms of the exercise training logs. While all subjects were informed to accurately and honestly write down and complete workouts following protocol, individuals could have been non-compliant. Most individuals, according to their exercise training logs, were within appropriate exercise intensity zones and stated that their diet remained mostly the same across the 8-week intervention. While HR monitors were used, and this helps to ensure more accurate results, subjects could have falsely written down information on the exercise training logs or skipped exercise sessions. Subjects were informed that if exercise sessions were missed due to personal reasons such as lack of time or sickness, to record this on the exercise training logs. A second limitation is differences in baseline measurements. While this thesis examined the effects of HIIT on healthy, sedentary individuals, this leaves a wide range of potential subjects, ranging from those who used to exercise and stopped for an extended period, to those who have never consistently exercised. Many individuals were young and overall in good physical shape while some other individuals who were also young, were classified as overweight or obese. These differences in baseline measurements could have confounded particular variables in this study. Third, while individuals who were placed into the control group were asked to maintain the current daily lifestyle throughout the 8-week intervention, there is the potential for error as some individuals may have exercised an extra session per week or stopped their current fitness levels altogether. Finally, while there was a total of 47 subjects that underwent pretest measurements, seven individuals withdrew from the study due to personal reasons, leaving only 40 individuals,

spread across evenly in each of the four groups, successfully completing the 8-week intervention. There was a challenge in recruiting subjects for this study due to several factors. The first being that this was not a financially compensated study. Second, an 8-week intervention is a long period of time and many felt they had too much stress in life with work, school, and/or family to participate. This study was recruiting individuals who were sedentary and asked them to potentially engage in strenuous exercise for an extended period of time. Many individuals who did not exercise stayed consistent with that decision and were not interested in beginning an exercise program.

References

1. Ziemann SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler Thromb Vasc Biol.* 2005;25(5):932-943. doi:10.1161/01.ATV.0000160548.78317.29.
2. O'Rourke MF, Hashimoto J. Mechanical Factors in Arterial Aging. A Clinical Perspective. *J Am Coll Cardiol.* 2007;50(1):1-13. doi:10.1016/j.jacc.2006.12.050.
3. O'Rourke MF, Hashimoto J. Arterial stiffness: A modifiable cardiovascular risk factor? *J Cardiopulm Rehabil Prev.* 2008;28(4):225-237. doi:10.1097/01.HCR.0000327179.21498.38.
4. Vaitkevicius P V, Fleg JL, Engel JH, et al. Effects of age and aerobic capacity on arterial stiffness in healthy adults. *Circulation.* 1993;88(4 Pt 1):1456-1462. doi:10.1161/01.cir.88.4.1456.
5. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and T of HBC in A (Adult TPI. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation.* 2002;106(25):3143-3421. doi:10.1007/BF02481509.
6. Blair SN. Physical Fitness and All-Cause Mortality. *JAMA.* 1989;262(17):2395. doi:10.1001/jama.1989.03430170057028.
7. Thum JS, Parsons G, Whittle T, Astorino TA. High-intensity interval training elicits higher enjoyment than moderate intensity continuous exercise. *PLoS One.* 2017;12(1). doi:10.1371/journal.pone.0166299.
8. Gibala MJ, Little JP, van Essen M, et al. Short-term sprint interval versus traditional endurance training: Similar initial adaptations in human skeletal muscle and exercise performance. *J Physiol.* 2006;575(3):901-911. doi:10.1113/jphysiol.2006.112094.
9. Hood MS, Little JP, Tarnopolsky MA, Myslik F, Gibala MJ. Low-volume interval training improves muscle oxidative capacity in sedentary adults. *Med Sci Sports Exerc.* 2011;43(10):1849-1856. doi:10.1249/MSS.0b013e3182199834.
10. Rognmo Ø, Hetland E, Helgerud J, Hoff J, Slørdahl S a. High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease. *Eur J Cardiovasc Prev Rehabil.* 2004;11(3):216-222. doi:10.1097/01.hjr.0000131677.96762.0c.
11. Wisloff U, Stoylen A, Loennechen JP, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a

- randomized study. *Circulation*. 2007;115(24):3086-3094. doi:10.1161/circulationaha.106.675041.
12. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics-2016 update a report from the American Heart Association. *Circulation*. 2016;133(4):e38-e48. doi:10.1161/CIR.0000000000000350.
 13. Franklin SS, Gustin W, Wong ND, et al. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation*. 1997;96(1):308-315. doi:10.1161/01.cir.96.1.308.
 14. Sutton-Tyrrell K, Najjar SS, Boudreau RM, et al. Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. *Circulation*. 2005;111(25):3384-3390. doi:10.1161/CIRCULATIONAHA.104.483628.
 15. Gkaliagkousi E, Douma S. The pathogenesis of arterial stiffness and its prognostic value in essential hypertension and cardiovascular diseases. *Hippokratia*. 2009;13(2):70-75.
 16. Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: implications for end-organ damage. *J Appl Physiol*. 2008;105(5):1652-1660. doi:10.1152/japplphysiol.90549.2008.
 17. Shirwany NA, Zou M. Arterial stiffness: a brief review. *Acta Pharmacol Sin*. 2010;31(10):1267-1276. doi:10.1038/aps.2010.123.
 18. Lakatta E. Cardiovascular Regulatory Mechanisms in Advanced Age. *Physiol Rev*. 1993;73(2):37-49. doi:10.1152/physrev.1993.73.2.413.
 19. Nagai Y, Metter EJ, Fleg JL. Increased carotid artery intimal-medial thickness: Risk factor for exercise-induced myocardial ischemia in asymptomatic older individuals. *Vasc Med*. 1999;4(3):181-186. doi:10.1177/1358836X9900400309.
 20. Kass DA. Age-related changes in ventricular-arterial coupling: Pathophysiologic implications. *Heart Fail Rev*. 2002;7(1):51-62. doi:10.1023/A:1013749806227.
 21. Currie KD, Thomas SG, Goodman JM. Effects of short-term endurance exercise training on vascular function in young males. *Eur J Appl Physiol*. 2009;107(2):211-218. doi:10.1007/s00421-009-1116-4.
 22. KIM H-K, HWANG C-L, YOO J-K, et al. All-Extremity Exercise Training Improves Arterial Stiffness in Older Adults. *Med Sci Sport Exerc*. 2017;49(7):1404-1411. doi:10.1249/MSS.0000000000001229.
 23. Hambrecht R, Fiehn E, Weigl C, et al. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. *Circulation*. 1998;98:2709-2715. doi:10.1161/01.CIR.98.24.2709.
 24. Hussain SR, Macaluso A, Pearson SJ. High-intensity interval training versus moderate-intensity continuous training in the prevention/management of cardiovascular disease. *Cardiol Rev*. 2016;24(6):273-281. doi:10.1097/CRD.0000000000000124.

25. Golbidi S, Laher I. Exercise and the cardiovascular system. *Cardiol Res Pract.* 2012;1(1). doi:10.1155/2012/210852.
26. Ciolac EG, Bocchi EA, Bortolotto LA, Carvalho VO, Greve JM, Guimarães G V. Effects of high-intensity aerobic interval training vs. moderate exercise on hemodynamic, metabolic and neuro-humoral abnormalities of young normotensive women at high familial risk for hypertension. *Hypertens Res.* 2010;33(8):836-843. doi:10.1038/hr.2010.72.
27. Ramos JS, Dalleck LC, Tjonna AE, Beetham KS, Coombes JS. The Impact of High-Intensity Interval Training Versus Moderate-Intensity Continuous Training on Vascular Function: a Systematic Review and Meta-Analysis. *Sport Med.* 2015;45(5):679-692. doi:10.1007/s40279-015-0321-z.
28. Molmen-Hansen HE, Stolen T, Tjonna AE, et al. Aerobic interval training reduces blood pressure and improves myocardial function in hypertensive patients. *Eur J Prev Cardiol.* 2012;19(2):151-160. doi:10.1177/1741826711400512.
29. Nichols WW, O'Rourke MF, Vlachopoulos C. *McDonald's Blood Flow in Arteries; Theoretical, Experimental and Clinical Principles.* Vol 23.; 1992. doi:10.1016/0306-3623(92)90079-Y.
30. Koch R, Sharma AM. Obesity and cardiovascular hemodynamic function. *Curr Hypertens Rep.* 1999;1(2):127-130. doi:10.1007/s11906-999-0006-9.
31. Bramwell JC, Hill A. VELOCITY OF TRANSMISSION OF THE PULSE-WAVE. *Lancet.* 1922;199(5149):891-892. doi:10.1016/S0140-6736(00)95580-6.
32. Santhanam L, Christianson DW, Nyhan D, Berkowitz DE. Arginase and vascular aging. *J Appl Physiol.* 2008;105(5):1632-1642. doi:10.1152/japplphysiol.90627.2008.
33. O'Rourke MF, Nichols WW. Aortic diameter, aortic stiffness, and wave reflection increase with age and isolated systolic hypertension. In: *Hypertension.* Vol 45. ; 2005:652-658. doi:10.1161/01.HYP.0000153793.84859.b8.
34. Celermajer DS, Sorensen KE, Bull C, Robinson J, Deanfield JE. Endothelium-dependent dilation in the systemic arteries of asymptomatic subjects relates to coronary risk factors and their interaction. *J Am Coll Cardiol.* 1994;24(6):1468-1474. doi:10.1016/0735-1097(94)90141-4.
35. Chantler PD, Frisbee JC. Arterial Function in Cardio-Metabolic Diseases: From the Microcirculation to the Large Conduits. *Prog Cardiovasc Dis.* 2015;57(5):489-496. doi:10.1016/j.pcad.2014.09.005.
36. Wilson MG, Ellison GM, Cable NT. Basic science behind the cardiovascular benefits of exercise. *Heart.* 2015. doi:10.1136/heartjnl-2014-306596.
37. Green DJ, Hopman MTE, Padilla J, Laughlin MH, Thijssen DHJ. Vascular Adaptation to Exercise in Humans: Role of Hemodynamic Stimuli. *Physiol Rev.* 2017.

doi:10.1152/physrev.00014.2016.

38. Berk BC, Min W, Yan C, Surapisitchat J, Liu Y, Hoefen RJ. Atheroprotective Mechanisms Activated by Fluid Shear Stress in Endothelial Cells. *Drug news Perspect.* 2002;15:133-139. <http://www.ncbi.nlm.nih.gov/pubmed/12677255>.
39. Donato AJ, Gano LB, Eskurza I, et al. Vascular endothelial dysfunction with aging: endothelin-1 and endothelial nitric oxide synthase. *Am J Physiol Heart Circ Physiol.* 2009;297(1):H425-32. doi:10.1152/ajpheart.00689.2008.
40. Lakatta EG, Levy D. Arterial and cardiac aging: Major shareholders in cardiovascular disease enterprises: Part I: Aging arteries: A “set up” for vascular disease. *Circulation.* 2003;107(1):139-146. doi:10.1161/01.CIR.0000048892.83521.58.
41. Avolio AP, Chen SG, Wang RP, Zhang CL, Li MF, O’Rourke MF. Effects of aging on changing arterial compliance and left ventricular load in a northern Chinese urban community. *Circulation.* 1983;68(1):50-58. doi:10.1161/01.CIR.68.1.50.
42. Epstein FH, Katz AM. Cardiomyopathy of Overload. *N Engl J Med.* 1990;322(2):100-110. doi:10.1056/NEJM199001113220206.
43. O’Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney: Cause and logic of therapy. In: *Hypertension.* Vol 46. ; 2005:200-204. doi:10.1161/01.HYP.0000168052.00426.65.
44. Greenberg SM. Small vessels, big problems. *N Engl J Med.* 2006;354:1451-1453. doi:10.1056/NEJMp068043.
45. Cullen KM, Kócsi Z, Stone J. Pericapillary haem-rich deposits: Evidence for microhaemorrhages in aging human cerebral cortex. *J Cereb Blood Flow Metab.* 2005;25(12):1656-1667. doi:10.1038/sj.jcbfm.9600155.
46. Hirata K, Yaginuma T, O’Rourke MF, Kawakami M. Age-related changes in carotid artery flow and pressure pulses: Possible implications for cerebral microvascular disease. *Stroke.* 2006;37(10):2552-2556. doi:10.1161/01.STR.0000242289.20381.f4.
47. Bortolotto LA, Hanon O, Franconi G, Boutouyrie P, Legrain S, Girerd X. The aging process modifies the distensibility of elastic but not muscular arteries. *Hypertension.* 1999;34(4 Pt 2):889-892. doi:10.1161/01.HYP.34.4.889.
48. Laurent S, Girerd X, Mourad JJ, et al. Elastic modulus of the radial artery wall material is not increased in patients with essential hypertension. *Arterioscler Thromb Vasc Biol.* 1994. doi:10.1161/01.ATV.14.7.1223.
49. Fleenor BS, Berrones AJ. *Arterial Stiffness Implications and Interventions.*; 2015.
50. Bank AJ, Wang H, Holte JE, Mullen K, Shammas R, Kubo SH. Contribution of Collagen, Elastin, and Smooth Muscle to In Vivo Human Brachial Artery Wall Stress and Elastic Modulus. *Circulation.* 1996;94(12):3263-3270. doi:10.1161/01.CIR.94.12.3263.

51. Dodson RB, Rozance PJ, Fleenor BS, et al. Increased arterial stiffness and extracellular matrix reorganization in intrauterine growth-restricted fetal sheep. *Pediatr Res*. 2013. doi:10.1038/pr.2012.156.
52. Fleenor BS. Large elastic artery stiffness with aging: novel translational mechanisms and interventions. *Aging Dis*. 2013.
53. Fleming I, Busse R. Signal transduction of eNOS activation. *Cardiovasc Res*. 1999;43(3):532-541. doi:10.1016/S0008-6363(99)00094-2.
54. Laurent S, Boutouyrie P, Asmar R, et al. Aortic Stiffness Is an Independent Predictor of All-Cause and Cardiovascular Mortality in Hypertensive Patients. *Hypertension*. 2001. doi:10.1161/01.HYP.37.5.1236.
55. Van Popele NM, Grobbee DE, Bots ML, et al. Association between arterial stiffness and atherosclerosis: The Rotterdam study. *Stroke*. 2001. doi:10.1161/01.STR.32.2.454.
56. Amar J, Ruidavets JB, Chamontin B, Drouet L, Ferrières J. Arterial stiffness and cardiovascular risk factors in a population-based study. *J Hypertens*. 2001. doi:http://dx.doi.org/10.1097/00004872-200103000-00005.
57. Meaume S, Rudnichi A, Lynch A, et al. Aortic pulse wave velocity as a marker of cardiovascular disease in subjects over 70 years old. *J Hypertens*. 2001. doi:10.1097/00004872-200105000-00006.
58. Willum-Hansen T, Staessen JA, Torp-Pedersen C, et al. Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation*. 2006;113(5):664-670. doi:10.1161/CIRCULATIONAHA.105.579342.
59. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. *Circulation*. 1999. doi:10.1161/01.CIR.99.18.2434.
60. Blacher J, Safar ME, Guerin a P, Pannier B, Marchais SJ, London GM. Aortic pulse wave velocity index and mortality in end-stage renal disease. *Kidney Int*. 2003. doi:kid932 [pii]\n10.1046/j.1523-1755.2003.00932.x.
61. Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: An integrated index of vascular function? *Circulation*. 2002. doi:10.1161/01.CIR.0000033824.02722.F7.
62. Boutouyrie P, Tropeano AI, Asmar R, et al. Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: a longitudinal study. *Hypertension*. 2002. doi:10.1161/hy0102.099031.
63. Mattace-Raso FUS, Van Der Cammen TJM, Hofman A, et al. Arterial stiffness and risk of coronary heart disease and stroke: The Rotterdam Study. *Circulation*. 2006;113(5):657-663. doi:10.1161/CIRCULATIONAHA.105.555235.

64. Weber T, Auer J, O'Rourke MF, et al. Arterial Stiffness, Wave Reflections, and the Risk of Coronary Artery Disease. *Circulation*. 2004. doi:10.1161/01.CIR.0000105767.94169.E3.
65. Lim HE, Park CG, Shin SH, Ahn JC, Seo HS, Oh DJ. Aortic pulse wave velocity as an independent marker of coronary artery disease. *Blood Press*. 2004. doi:10.1080/08037050410004800.
66. Mitchell GF, Izzo JL, Lacourcière Y, et al. Omapatrilat reduces pulse pressure and proximal aortic stiffness in patients with systolic hypertension: Results of the conduit hemodynamics of omapatrilat international research study. *Circulation*. 2002. doi:10.1161/01.CIR.0000020500.77568.3C.
67. Mitchell GF, Conlin PR, Dunlap ME, et al. Aortic diameter, wall stiffness, and wave reflection in systolic hypertension. *Hypertension*. 2008. doi:10.1161/HYPERTENSIONAHA.107.099721.
68. Gurovich AN, Beck DT, Braith RW. Aortic Pulse Wave Analysis is not a surrogate for central arterial Pulse Wave Velocity. *Exp Biol Med (Maywood)*. 2009. doi:10.3181/0902-RM-88.
69. Mitchell GF, Hwang S-J, Vasan RS, et al. Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation*. 2010;121(4):505-511. doi:10.1161/CIRCULATIONAHA.109.886655.
70. Donley D a, Fournier SB, Reger BL, et al. Aerobic exercise training reduces arterial stiffness in metabolic syndrome. *J Appl Physiol*. 2014. doi:10.1152/jappphysiol.00151.2014.
71. O'Rourke MF, Staessen JA, Vlachopoulos C, Duprez D, Plante GE. Clinical applications of arterial stiffness; definitions and reference values. *Am J Hypertens*. 2002. doi:10.1016/S0895-7061(01)02319-6.
72. Murgu JP, Westerhof N, Giolma JP, Altobelli SA. Aortic input impedance in normal man: Relationship to pressure wave forms. *Circulation*. 1980. doi:10.1161/01.CIR.62.1.105.
73. Hirata K, Kawakami M, O'Rourke MF. Pulse wave analysis and pulse wave velocity: a review of blood pressure interpretation 100 years after Korotkov. *Circ J*. 2006;70(10):1231-1239. doi:10.1152/ajpheart.00443.2011.
74. McEniery CM, Cockcroft JR, Roman MJ, Franklin SS, Wilkinson IB. Central blood pressure: Current evidence and clinical importance. *Eur Heart J*. 2014. doi:10.1093/eurheartj/eh565.
75. Nichols WW, Singh BM. Augmentation index as a measure of peripheral vascular disease state. *Curr Opin Cardiol*. 2002. doi:10.1097/00001573-200209000-00016.
76. Halcox JPJ, Schenke WH, Zalos G, et al. Prognostic value of coronary vascular endothelial dysfunction. *Circulation*. 2002. doi:10.1161/01.CIR.0000025404.78001.D8.
77. Fleming I, Busse R. Molecular mechanisms involved in the regulation of the endothelial

- nitric oxide synthase. *Am J Physiol Regul Integr Comp Physiol*. 2003. doi:10.1152/ajpregu.00323.2002.
78. Powell KE, Paluch AE, Blair SN. Physical Activity for Health: What Kind? How Much? How Intense? On Top of What? *Annu Rev Public Health*. 2011. doi:10.1146/annurev-publhealth-031210-101151.
 79. Laursen PB, Jenkins DG. The scientific basis for high-intensity interval training: Optimising training programmes and maximising performance in highly trained endurance athletes. *Sport Med*. 2002. doi:10.2165/00007256-200232010-00003.
 80. Londeree BR. Effect of training on lactate/ventilatory thresholds: A meta-analysis. *Med Sci Sports Exerc*. 1997. doi:10.1097/00005768-199706000-00016.
 81. Hickson RC, Bomze H a, Holloszy JO. Linear increase in aerobic power induced by a strenuous program of endurance exercise. *J Appl Physiol*. 1977. doi:10.1152/jappl.1977.42.3.372.
 82. Belcastro AN, Bonen A. Lactic acid removal rates during controlled and uncontrolled recovery exercise. *J Appl Physiol*. 1975;39(6):932-936.
 83. Bond B, Hind S, Williams CA, Barker AR. The Acute Effect of Exercise Intensity on Vascular Function in Adolescents. *Med Sci Sports Exerc*. 2015;47(12):2628-2635. doi:10.1249/MSS.0000000000000715.
 84. Green HJ, Jones LL, Houston ME, Ball-Burnett ME, Farrance BW. Muscle energetics during prolonged cycling after exercise hypervolemia. *J Appl Physiol*. 1989;66(2):622-631. doi:10.1152/jappl.1989.66.2.622.
 85. Green HJ, Jones LL, Painter DC. Effects of short-term training on cardiac function during prolonged exercise. *Med Sci Sports Exerc*. 1990;22(4):488-493. doi:10.1249/00005768-199008000-00012.
 86. Green HJ, Coates G, Sutton JR, Jones S. Early adaptations in gas exchange, cardiac function and haematology to prolonged exercise training in man. *Eur J Appl Physiol Occup Physiol*. 1991;63(1):17-23. doi:10.1007/BF00760795.
 87. Vock R, Hoppeler H, Claassen H, et al. Design of the oxygen and substrate pathways VI. Structural basis of intracellular substrate supply to mitochondria in muscle cells. *J Exp Biol*. 1996;199(Pt 8):1689-1697.
 88. Coggan AR. Plasma glucose metabolism during exercise: effect of endurance training in humans. *Med Sci Sports Exerc*. 1997;29(5):620-627. <http://www.ncbi.nlm.nih.gov/pubmed/9140898>.
 89. Martin WH, Dalsky GP, Hurley BF, et al. Effect of endurance training on plasma free fatty acid turnover and oxidation during exercise. *Am J Physiol*. 1993;265(5 Pt 1):E708-E714. doi:10.1152/ajpendo.1993.265.5.E708.
 90. Wadley AJ, Chen Y-W, Lip GYH, Fisher JP, Aldred S. Low volume-high intensity interval

- exercise elicits antioxidant and anti-inflammatory effects in humans. *J Sports Sci.* 2015;414(May 2015):1-9. doi:10.1080/02640414.2015.1035666.
91. Little JP, Gillen JB, Percival ME, et al. Low-volume high-intensity interval training reduces hyperglycemia and increases muscle mitochondrial capacity in patients with type 2 diabetes. *J Appl Physiol.* 2011. doi:10.1152/jappphysiol.00921.2011.
 92. WHO. Obesity and overweight: Fact sheet No 311. 311. <http://www.who.int/mediacentre/factsheets/fs311>. Published 2016.
 93. Shaw K, Gennat H, O'Rourke P, Del Mar C. Exercise for overweight or obesity. *Cochrane Database Syst Rev.* 2006;(4). doi:10.1002/14651858.CD003817.pub3.
 94. King NA. What processes are involved in the appetite response to moderate increases in exercise-induced energy expenditure? *Proc Nutr Soc.* 1999;58(1):107-113. doi:10.1079/PNS19990015.
 95. Wewege M, van den Berg R, Ward RE, Keech A. The effects of high-intensity interval training vs. moderate-intensity continuous training on body composition in overweight and obese adults: a systematic review and meta-analysis. *Obes Rev.* 2017;18(6):635-646. doi:10.1111/obr.12532.
 96. Hwang C-L, Yoo J-K, Kim H-K, et al. Novel all-extremity high-intensity interval training improves aerobic fitness, cardiac function and insulin resistance in healthy older adults. *Exp Gerontol.* 2016;82:112-119. doi:10.1016/j.exger.2016.06.009.
 97. Wewege M, van den Berg R, Ward RE, Keech A. The effects of high-intensity interval training vs. moderate-intensity continuous training on body composition in overweight and obese adults: a systematic review and meta-analysis. *Obes Rev.* 2017;18(6):635-646. doi:10.1111/obr.12532.
 98. Millet GP, Vleck VE, Bentley DJ. Physiological differences between cycling and running: Lessons from triathletes. *Sport Med.* 2009;39(3):179-206. doi:10.2165/00007256-200939030-00002.
 99. Kochanek KD, Murphy SL, Xu M.D. J, Arias Ph.D. E. Mortality in the United States, 2013. *NCHS Data Brief; No 178.* 2014. doi:10.1056/NEJM184002260220306.
 100. Chae CU, Pfeffer M a, Glynn RJ, Mitchell GF, Taylor JO, Hennekens CH. Increased pulse pressure and risk of heart failure in the elderly. *Jama.* 1999;281(7):634-639. doi:joc80370 [pii].
 101. Vigen R, Maddox TM, Allen LA. Aging of the united states population: Impact on heart failure. *Curr Heart Fail Rep.* 2012;9(4):369-374. doi:10.1007/s11897-012-0114-8.
 102. McEniery CM, Wilkinson IB, Avolio AP. Age, hypertension and arterial function. *Clin Exp Pharmacol Physiol.* 2007;34(7):665-671. doi:10.1111/j.1440-1681.2007.04657.x.
 103. Karim-Kos HE, de Vries E, Soerjomataram I, Lemmens V, Siesling S, Coebergh JWW. Recent trends of cancer in Europe: A combined approach of incidence, survival and

- mortality for 17 cancer sites since the 1990s. *Eur J Cancer*. 2008;44(10):1345-1389. doi:10.1016/j.ejca.2007.12.015.
104. Steppan J, Barodka V, Berkowitz DE, Nyhan D. Vascular Stiffness and Increased Pulse Pressure in the Aging Cardiovascular System. *Cardiol Res Pract*. 2011;2011:1-8. doi:10.4061/2011/263585.
 105. Merillon JP, Fontenier GJ, Lerallut JF, et al. Aortic input impedance in normal man and arterial hypertension: Its modification during changes in aortic pressure. *Cardiovasc Res*. 1982;16(11):646-656. doi:10.1093/cvrese/16.11.646.
 106. Asmar R, Benetos A, London G, et al. Aortic distensibility in normotensive, untreated and treated hypertensive patients. *Blood Press*. 1995;4(1):48-54. doi:10.3109/08037059509077567.
 107. Hasegawa M, Nagao K, Kinoshita Y, Rodbard D, Asahina A. Increased pulse wave velocity and shortened pulse wave transmission time in hypertension and aging. *Cardiol*. 1997;88(2):147-151. doi:10.1159/000177321.
 108. Harvey A, Montezano AC, Touyz RM. Vascular biology of ageing-Implications in hypertension. *J Mol Cell Cardiol*. 2015;83:112-121. doi:10.1016/j.yjmcc.2015.04.011.
 109. Lee IM, Shiroma EJ, Lobelo F, et al. Effect of physical inactivity on major non-communicable diseases worldwide: An analysis of burden of disease and life expectancy. *Lancet*. 2012;380(9838):219-229. doi:10.1016/S0140-6736(12)61031-9.
 110. Resnick HE, Foster GL, Bardsley J, Ratner RE. Achievement of American Diabetes Association clinical practice recommendations among U.S. adults with diabetes, 1999-2002: The National Health and Nutrition Examination Survey. *Diabetes Care*. 2006;29(3):531-537. doi:10.2337/diacare.29.03.06.dc05-1254.
 111. Kannel WB, McGee DL. Diabetes and cardiovascular risk factors: The Framingham study. *Circulation*. 1979;59(1):8-13. doi:10.1161/01.CIR.59.1.8.
 112. Cameron JD, Cruickshank JK. Glucose, insulin, diabetes and mechanisms of arterial dysfunction. *Clin Exp Pharmacol Physiol*. 2007;34(7):677-682. doi:10.1111/j.1440-1681.2007.04659.x.
 113. Schram MT, Kostense PJ, Van Dijk RAJM, et al. Diabetes, pulse pressure and cardiovascular mortality: The Hoorn Study. *J Hypertens*. 2002;20(9):1743-1751. doi:10.1097/00004872-200209000-00017.
 114. Safar ME. Obesity, Arterial Stiffness, and Cardiovascular Risk. *J Am Soc Nephrol*. 2006;17(4_suppl_2):S109-S111. doi:10.1681/ASN.2005121321.
 115. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of All-Cause Mortality With Overweight and Obesity Using Standard Body Mass Index Categories. *JAMA*. 2013;309(1):71. doi:10.1001/jama.2012.113905.
 116. Pierce GL, Zhu H, Darracott K, et al. Arterial stiffness and pulse-pressure amplification in

- overweight/obese African-American Adolescents: Relation with higher systolic and pulse pressure. *Am J Hypertens*. 2013;26(1):20-26. doi:10.1093/ajh/hps014.
117. Orr JS, Gentile CL, Davy BM, Davy KP. Large Artery Stiffening With Weight Gain in Humans. *Hypertension*. 2008;51(6):1519-1524. doi:10.1161/01.hyp.34.2.201.
 118. Huynh Q, Blizzard L, Sharman J, et al. Relative contributions of adiposity in childhood and adulthood to vascular health of young adults. *Atherosclerosis*. 2013;228(1):259-264. doi:10.1016/j.atherosclerosis.2013.02.022.
 119. R.J. V, M.F. M, D.J. G, A.R. H, M.T. H, D.H. T. A systematic review and meta-analysis on the effects of exercise training versus hypocaloric diet: Distinct effects on body weight and visceral adipose tissue. *Obes Facts*. 2015;8(9):217. doi:10.1111/obr.12406.
 120. Cooper JN, Buchanich JM, Youk A, et al. Reductions in arterial stiffness with weight loss in overweight and obese young adults: Potential mechanisms. *Atherosclerosis*. 2012;223(2):485-490. doi:10.1016/j.atherosclerosis.2012.05.022.
 121. Ding D, Lawson KD, Kolbe-Alexander TL, et al. The economic burden of physical inactivity: a global analysis of major non-communicable diseases. *Lancet*. 2016;388(10051):1311-1324. doi:10.1016/S0140-6736(16)30383-X.
 122. Tanaka H, DeSouza CA, Seals DR. Absence of age-related increase in central arterial stiffness in physically active women. *Arterioscler Thromb Vasc Biol*. 1998;18(1):127-132. doi:10.1161/01.ATV.18.1.127.
 123. Quan HL, Blizzard CL, Sharman JE, et al. Resting heart rate and the association of physical fitness with carotid artery stiffness. *Am J Hypertens*. 2014;27(1):65-71. doi:10.1093/ajh/hpt161.
 124. Zhu W, Hooker SP, Sun Y, Xie M, Su H, Cao J. Associations of cardiorespiratory fitness with cardiovascular disease risk factors in middle-aged Chinese women: A cross-sectional study. *BMC Womens Health*. 2014;14(1). doi:10.1186/1472-6874-14-62.
 125. Tjonna AE, Lee SJ, Rognmo O, et al. Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study. *Circulation*. 2008;118:346-354. doi:CIRCULATIONAHA.108.772822 [pii]\r10.1161/CIRCULATIONAHA.108.772822.
 126. Nezu T, Hosomi N, Aoki S, Matsumoto M. Carotid Intima-Media Thickness for Atherosclerosis. *J Atheroscler Thromb*. 2016. doi:10.5551/jat.31989.
 127. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: A systematic review and meta-analysis. *Circulation*. 2007. doi:10.1161/CIRCULATIONAHA.106.628875.
 128. Crouse JR, Goldbourt U, Evans G, et al. Arterial enlargement in the atherosclerosis risk in communities (ARIC) cohort. In vivo quantification of carotid arterial enlargement. The ARIC Investigators. *Stroke*. 1994. doi:10.1161/01.STR.25.7.1354.

129. Handa N, Matsumoto M, Maeda H, et al. Ultrasonic evaluation of early carotid atherosclerosis. *Stroke*. 1990. doi:10.1161/01.STR.21.11.1567.
130. Guimaraes G V, Ciolac EG, Carvalho VO, D'Avila VM, Bortolotto LA, Bocchi EA. Effects of continuous vs. interval exercise training on blood pressure and arterial stiffness in treated hypertension. *HypertensRes*. 2010;33(1348-4214 (Electronic)):627-632. doi:10.1038/hr.2010.42.
131. Siasos G, Athanasiou D, Terzis G, et al. Acute effects of different types of aerobic exercise on endothelial function and arterial stiffness. *Eur J Prev Cardiol*. 2016;23(14):1565-1572. doi:10.1177/2047487316647185.
132. Wisloff U, Stoylen A, Loennechen JP, et al. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. *Circulation*. 2007;115(24):3086-3094. doi:10.1161/circulationaha.106.675041.
133. Hwang C-L, Yoo J-K, Kim H-K, et al. Novel all-extremity high-intensity interval training improves aerobic fitness, cardiac function and insulin resistance in healthy older adults. *Exp Gerontol*. 2016;82:112-119. doi:10.1016/j.exger.2016.06.009.
134. Matsuo T, Saotome K, Seino S, et al. Effects of a low-volume aerobic-type interval exercise on $\dot{V}O_{2\max}$ and cardiac mass. *Med Sci Sports Exerc*. 2014;46(1):42-50. doi:10.1249/MSS.0b013e3182a38da8.
135. Tjonna AE, Lee SJ, Rognmo O, et al. Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome: a pilot study. *Circulation*. 2008;118:346-354. doi:CIRCULATIONAHA.108.772822 [pii]r10.1161/CIRCULATIONAHA.108.772822.
136. Currie KD, Dubberley JB, McKelvie RS, Macdonald MJ. Low-volume, high-intensity interval training in patients with CAD. *Med Sci Sports Exerc*. 2013;45(8):1436-1442. doi:10.1249/MSS.0b013e31828bbbd4.
137. Foster C, Farl C V., Guidotti F, et al. The effects of high intensity interval training vs steady state training on aerobic and anaerobic capacity. *J Sport Sci Med*. 2015;14(4):747-755. doi:10.1249/01.mss.0000476771.63318.52.
138. Loftin M, Sothorn M, Warren B, Udall J. Comparison of $\dot{V}O_{2\text{peak}}$ during treadmill and cycle ergometry in severely overweight youth. *J Sport Sci Med*. 2004;3(4):254-260.
139. Pechar G, McArdle W, Katch F, Magel J DJ. Specificity of cardiorespiratory adaptation to bicycle and treadmill training. *J Appl Physiol*. 1974;36:753-756.
140. Sijie T, Hainai Y, Fengying Y, Jianxiong W. High intensity interval exercise training in overweight young women. *J Sports Med Phys Fitness*. 2012;52(3):255-262. doi:10.1519/JSC.0000000000000335.
141. Tagawa K, Choi Y, Ra S-G, Yoshikawa T, Kumagai H, Maeda S. Resistance training-induced

- decrease in central arterial compliance is associated with decreased subendocardial viability ratio in healthy young men. *Appl Physiol Nutr Metab*. 2017. doi:10.1139/apnm-2017-0449.
142. Miyachi M, Kawano H, Sugawara J, et al. Unfavorable effects of resistance training on central arterial compliance: A randomized intervention study. *Circulation*. 2004;110(18):2858-2863. doi:10.1161/01.CIR.0000146380.08401.99.
 143. Cortez-Cooper MY, DeVan AE, Anton MM, et al. Effects of high intensity resistance training on arterial stiffness and wave reflection in women. *Am J Hypertens*. 2005;18(7):930-934. doi:10.1016/j.amjhyper.2005.01.008.
 144. Au JS, Oikawa SY, Morton RW, MacDonald MJ, Phillips SM. Arterial Stiffness Is Reduced Regardless of Resistance Training Load in Young Men. *Med Sci Sports Exerc*. 2017. doi:10.1249/MSS.0000000000001106.
 145. Sacre JW, Jennings GLR, Kingwell BA. Exercise and dietary influences on arterial stiffness in cardiometabolic disease. *Hypertension*. 2014. doi:10.1161/HYPERTENSIONAHA.113.02277.