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Boxing Training Effects on Cardiovascular Risk, Quality of Life, Endothelial Function, and Blood Flow Patterns in Individuals with Elevated Blood Pressure or Stage 1 Hypertension

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ABSTRACT

Early stages of high blood pressure, such as elevated blood pressure or stage 1 hypertension, have shown to increase cardiovascular mortality. Exercise is recommended for the prevention and treatment of high blood pressure; however, most clinical evidence is based on traditional types of exercise that have relatively high dropout rates. Therefore, the purpose of this study was to evaluate the effects of boxing training, a nontraditional exercise modality, on clinical and vascular outcomes and its relation to blood flow patterns in individuals with elevated blood pressure or stage 1 hypertension. To achieve these goals, two experiments were designed. The first one, a randomized controlled trial, evaluated the effects of boxing training on brachial blood pressure, central blood pressure, arterial stiffness, cardiorespiratory fitness, cardiac adaptations, body composition, lipid profile, quality of life, vascular adaptations, nitric oxide bioavailability, inflammation, and oxidative stress in individuals with elevated blood pressure or stage 1 hypertension. The main findings were that 6 weeks of boxing training, with a polarized intensity regime, in individuals with elevated blood pressure or stage 1 hypertension improved clinical outcomes, such as peripheral and central blood pressure, resting heart rate, myocardial wall thickness, VO_2max, ventilatory and lactate thresholds, and quality of life, and vascular outcomes, such as conduit artery endothelial function, resistance vessels structure and endothelial function, and carotid artery structure. All these changes were linked to an increased nitric oxide bioavailability and a reduction in inflammation. The second one, a cross-sectional study, confirmed that endothelial shear stress in the common carotid artery increased during boxing training in individuals with elevated blood pressure or stage 1 hypertension.

Altogether, we proposed that boxing training is a suitable alternative for the management of elevated blood pressure and stage 1 hypertension.

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CHAPTER 1: INTRODUCTION, STATEMENT OF PURPOSE, AND SPECIFIC AIMS

1.1. Introduction

1.1.1. Introduction and Significance

Cardiovascular diseases (CVD) such as coronary artery disease, heart failure, peripheral artery disease, and stroke are the leading cause of death in the US and worldwide. CVD are responsible for 17.3 million deaths, which account a third of all global causes of death, which accounts [1]. Additionally, CVD are the second most common cause of disability in the US, with a 16.8% of total disability-adjusted life-years (DALYs) [2,3], and the first cause of global disability, with an 11.8% of total DALYs [4].

Nearly 92.1 million US adults suffer from at least one type of CVD, which represents 36.6% of the entire US adult population. According to the projections of the American Heart Association (AHA), a 7.3% growth is expected by 2030. The total cost of CVD is approximately $316.1 billion; according to the projections for 2030, direct and indirect costs will reach $818 billion and $276 billion, respectively [1].

Several risk factors have been associated to CVD, such as high blood pressure, obesity dyslipidemia, impaired fasting glucose, sedentary behavior, and physical inactivity [5]. Among all these cardiovascular risk factors, high blood pressure is the most prevalent [6]. Taking into consideration the current ACC/AHA classification, approximately 46% of the total US adult population (116 million) are diagnosed with hypertension [7]. Apart from being a risk factor for the development of CVD, high blood pressure affects several organs (e.g. chronic kidney disease, retinopathy, and cognitive impairment) [8]. By itself, high blood pressure accounts for 34.1% of all deaths in US adults, with the estimated total cost of medical treatment for high

blood pressure in the country at $52.1 billion. If no action is taken, the total cost of high blood pressure treatment and management within the US will be around $200 billion by 2030 [1].

Elevated blood pressure or stage 1 hypertension are categories of high blood pressure formerly known as prehypertension. The prevalence of both categories ranges from 22% to 38%. The main feature of relevance for these categories is the risk of progression to more severe high blood pressure stages, which have been estimated to be two- to three-fold higher in comparison to normotensive adults [9-13]. Moreover, compared to subjects with optimal blood pressure, those with elevated blood pressure or stage 1 hypertension have an estimated increased risk of 50%, 71%, 55%, and 66% for coronary artery disease, stroke, CVD-related morbidity and CVD-related mortality, respectively [14-16].

Individuals with elevated blood pressure or stage 1 hypertension without an estimated 10-year risk of CVD of ≥10%, as calculated by the ACC/AHA Pooled Cohort Equations, are not candidates for drug treatment. In turn, management strategies for this population primarily include lifestyle modifications, such as the incorporation of an exercise training program [7,9,17]. Current medical guidelines have established that exercise is a cornerstone in high blood pressure prevention and treatment and its effectiveness is comparable to drug treatment [7,18]. Indeed, for every dollar invested in strategies to incorporate physical activity as a preventive cardiovascular tool, there is a return of approximately three to six dollars in terms of healthcare costs [1,19]. However, the optimal exercise prescription dose for high blood pressure and the mechanisms behind the health benefits of exercise are have not yet fully been clarified [20,21].

1.1.2. Background

High blood pressure is an operational definition that relates in a log-linear manner the levels of brachial blood pressure to organ damage, morbidity, and mortality [7]. Several pathological features are involved and interconnected in the development of high blood pressure, such as endothelial dysfunction, oxidative stress, inflammation, autonomic dysfunction, an overreactive renin-angiotensin-aldosterone pathway, and arterial stiffness [8]. Endothelial dysfunction appears to have a central role in the progression to high blood pressure according to the Mosaic Theory, mainly by affecting the ability of the vessels to maintain homeostasis [22]. Endothelial dysfunction can be identified by one or more of the following characteristics: (1) a decline in nitric oxide (NO) bioavailability and subsequent impaired vasodilation, (2) upregulation of adhesion molecules and inflammatory genes, (3) oxidant stress exacerbation, and (4) increased permeability of the endothelial barrier [23]. Additionally, the decreased NO bioavailability produces a cascade of events including oxidation of low-density lipoprotein cholesterol (LDL-C), leukocyte recruitment, and foam cell formation which becomes the basis of atherosclerotic plaque formation [24,25]. Meanwhile, arterial stiffness directly impacts blood pressure by affecting afterload and arterial-ventricular coupling [26,27].

Exercise training has shown to be beneficial to prevent or treat CVD and to improve cardiovascular risk factors. Specifically, exercise training is a recommendation class IA for individuals with individuals with elevated blood pressure or stage 1 hypertension [7]. A class IA recommendation is the strongest recommendation given for a treatment that is based on multiple randomized controlled trials or meta-analyses [6]. Meta-analyses have described that exercise significantly improves brachial blood pressure [18,28,29], central blood pressure [30], cardiorespiratory fitness [31], arterial stiffness [32], the lipid profile, and body composition [31]

in individuals with high blood pressure. Additionally, exercise training can target cellular pathways involved with high blood pressure and produce favorable adaptations in the structure and function of the heart and vessels [21,33]. The cardiovascular health benefits of exercise go beyond the reduction of cardiovascular risk factors [20]. Endothelial shear stress has been recognized as a mechanism that modulates endothelial gene expression through mechanotransduction [34]. Exercise-induced shear stress has been related to favorable cardiovascular adaptations but the evidence related to this topic is based on limited exercise modalities (e.g. running, cycling, or resistance training) [21].

Even though the beneficial effects of exercise on health are well known, only 21.6% of the US adult population cover the minimal weekly recommendations [1]. Moreover, CVD patients are not that committed to incorporate exercise as part of their cardiac rehabilitation programs as dropout rates from cardiac rehabilitation programs has been estimated as high as 80% [35-37]. Multiple factors affect the decision to adhere an exercise program, such as personality, personal preferences, and organizational characteristics [38-42]. The incorporation of more exercise alternatives (e.g. nontraditional modalities) to traditional physical activity programs (e.g. walking, running, cycling, and resistance training) might attract more people and increase the retention [35,43,44]. However, before a nontraditional modality of exercise can be recommended for health-related purposes, it should be supported by a solid scientific evidence [45].

Boxing training is a type of exercise that involves high cardiovascular demands, high-impact punching, and coordinated movements in an enjoyable environment [46-48]. Previously, boxing training has shown to have excellent motor outcomes in stroke [49] and Parkinson's disease patients[50,51]. Nonetheless, research regarding the effects of boxing training on

cardiovascular health is scarce [52,53]. To date, no randomized controlled trial employing boxing training as an intervention has been executed in individuals with high blood pressure.

1.2. Statement of Purpose

The purpose of this dissertation was to describe the effects of boxing training on cardiovascular risk and vascular health and its relationship with blood flow in individuals with elevated blood pressure or stage 1 hypertension. To achieve these goals, two experimental designs were applied. First, a randomized controlled trial to evaluate the effects of boxing training on cardiovascular risk and vascular health in individuals with elevated blood pressure or stage 1 hypertension were employed. Second, in a cross-sectional study we characterized *in vivo* common carotid artery blood flow patterns in individuals with elevated blood pressure or stage 1 hypertension during boxing drills.

1.3. Specific Aims and Hypotheses

1.3.1. Experiment 1

Specific Aim 1. To determine whether boxing training reduces cardiovascular risk in individuals with elevated blood pressure or stage 1 hypertension.

Hypothesis 1. Boxing training, 3 days per week for 6 weeks will reduce cardiovascular risk in individuals with elevated blood pressure or stage 1 hypertension.

To asses cardiovascular risk factors, the following clinical outcomes will be evaluated:

- Brachial Blood Pressure
- Central Blood Pressure
- Arterial Stiffness

- Cardiorespiratory Fitness
- Structural Cardiac Adaptations
- Body Composition
- Lipid Profile
- Quality of Life

Specific Aim 2. To determine whether boxing training will improve vascular health in individuals with elevated blood pressure or stage 1 hypertension.

Hypothesis 2. Boxing training 3 days per week for 6 weeks will improve vascular health in individuals with elevated blood pressure or stage 1 hypertension.

To asses vascular health, the following variables will be evaluated:

- Endothelial Function and Structure of Conduit Arteries
- Endothelial Function and Structure of Resistance Vessels
- Nitric Oxide Bioavailability
- Inflammation
- Oxidative Stress

1.3.2. Experiment 2

Specific Aim 3. To characterize blood flow in the carotid artery during boxing training activities in individuals with elevated blood pressure or stage 1 hypertension.

Hypothesis 3. Anterograde endothelial shear stress will be turbulent and will increase during boxing training activities in comparison to resting conditions.

The following blood flow characteristics will be analyzed:

- Direction
- Endothelial Shear Stress magnitude
- Patterns (presence of turbulence)

CHAPTER 2: LITERATURE REVIEW

2.1. The Cardiovascular System

The human cardiovascular system is composed of the heart, the vasculature, and the blood. The main functions of this organ system are to: (1) coordinate the transport and delivery of respiratory gases, nutrients, waste products, and other chemical messengers, (2) maintain homeostasis (e.g., liquids, pH, temperature, blood pressure, etc.), and (3) protect the body from hemorrhage and infections. This system can be functionally divided into two circuits: the systemic left-circulation and the pulmonary right-circulation. In the systemic circulation, the left atrium receives oxygenated blood from the pulmonary veins, then the blood accesses the left ventricle where it is ejected into the aorta to reach organs, while deoxygenated blood returns to the heart. In the pulmonary circulation, the deoxygenated blood in the right atrium travels to the right ventricle and it is pumped to the lungs for gas exchange and the oxygenated blood returns to the heart [54].

The heart is a hollow, muscular, pulsatile blood pump connected to the vascular tree. This organ can generate and control its own pace through a pacemaker, localized in the right atrium (the sinoatrial node), and a conduction system (the atrioventricular node, bundle of his, and Purkinje fibers). Additionally, there is an external control provided by the autonomic nervous system (sympathetic and parasympathetic) and the endocrine system (e.g. catecholamines) [55].

A blood vessel is a tube-like structure whose wall is generally comprised of three layers: the intima, the media, and the adventitia. The intima is the innermost layer composed of a monolayer of endothelial cells, connective tissue located at the subendothelial space, and an elastic internal membrane. The media is enclosed by the internal and external elastic membranes, contains smooth muscle cells and extracellular matrix (e.g. elastin and collagen) and provides the contractile

and elastic properties of the vessels. The adventitia is the outer layer composed of fibroblasts, connective tissue, perivascular nerves, and the vasa vasorum [56]. Blood vessels can be classified based on their structure and function in elastic arteries, muscular arteries, resistance vessels, exchange vessels, and capacitance vessels. Elastic or central arteries (e.g. aorta) are the largest of all vessels and their great distensibility is a key feature to maintain blood flow during diastole. Muscular or conduit arteries (e.g., brachial, carotid, brachial, and popliteal) are medium-sized vessels that direct blood towards smaller branches and constantly adapt their diameters by smooth muscle relaxation or contraction. Resistance vessels (e.g. terminal arteries and arterioles) are the central governor of vascular peripheral resistance. Exchange vessels (e.g. capillaries) are the smallest vessels and are the site of gas and metabolite exchange. Finally, capacitance vessels (e.g. venules and veins) contain most of the blood under resting conditions and can rapidly accommodate changes in blood volume according to metabolic requirements. The size, composition, and main function of each vessel are depicted in Table 1.

Table 1. Blood vessels structure and function

	Diameter (mm)	Wall thickness (mm)	Endothelial cells (%)	Elastic tissue (%)	Smooth muscle (%)	Fibrous tissue (%)	Main Function
Elastic arteries	15	1	5	60	25	20	Pulse dampener
Muscular arteries	5	1	5	13	65	20	Distribution
Arterioles	0.03	0.006	10	10	60	20	Resistance
Capillaries	0.009	0.0005	95	0	0	5	Gas exchange
Venules	0.02	0.001	20	0	20	60	Capacitance
Veins	5	0.5	10	5	30	60	Blood return

Note. Adapted from Smith and Fernhall [54].

The blood is a body fluid that circulates throughout the body and is composed by blood cells (e.g., erythrocytes, leukocytes, and thrombocytes) and plasma. Erythrocytes transport oxygen from the lungs to capillaries, leukocytes modulate the immune system and inflammation, and thrombocytes initiate blood clot formation. Plasma is the fluid portion in which blood cells are

suspended and contains water, proteins, signaling molecules, cell-derived vesicles, nutrients, electrolytes, oxygen, dioxide oxygen, and hormones [54].

2.2. Basic Hemodynamic Concepts

2.2.1. Preload

Preload comprises all the factors that contribute to passive ventricular wall stress at end-diastole and can be expressed according to LaPlace's Law, T=$PxR/2$ for thin-walled spheres, where T is tension, P is chamber pressure, and R is radius. For thick-walled spheres like the left ventricle, it can be expressed as σ=$PxR/2w$, where σ is wall stress and *w* is wall thickness. The factors that determine end-diastolic radius are the compliance of the ventricle and pericardium. End-diastolic filling pressure is dependent on total blood volume, blood volume distribution, atrial contraction, venous compliance, total peripheral resistance, and venous return. Finally, myocardial wall thickness relies on the state of the individual, for example, long-term high blood pressure is associated with left ventricular hypertrophy (LVH). End-diastolic left ventricular pressure and volume are surrogate measurements employed in clinical practice to estimate preload [57].

2.2.2. Afterload

Afterload is the force against which the heart has to contract to eject the blood. Other definitions include the stress that the left ventricle experiences when it contracts against the end-diastolic volume or as arterial input impedance. Total peripheral resistance and arterial compliance are main features of afterload. The arterioles are recognized as the site that determines peripheral resistance which in turn are controlled by the autonomic nervous system

(sympathetic/parasympathetic balance) and local mediators like NO. Arterial compliance refers to the ability of the vessel to expand and contract passively with changes in pressure and is an index of elasticity. The elastic component of the vascular wall is affected by age and pathological conditions like high blood pressure, which is translated into stiffer arteries and a long-term afterload mismatch that can induce LVH, among other complications [58].

2.2.3. Contractility

Contractility, also known as inotropy, is the inherant capacity of the cardiac muscle to contract independently of preload and afterload and is an expression of the cellular mechanisms involved with muscle contraction (e.g. excitation-contraction coupling, sarcomere shortening and subsequent relaxation). From a clinical standpoint, contractility is determined by a change in work (e.g. left ventricular change in pressure per time, dP/dt) at a fixed end-diastolic volume and aortic pressure. Ejection fraction (EF) measured by echocardiography and dP/dt_{max} measured during cardiac catheterization are indexes of contractility. EF less than 55% and dP/dt_{max} less than 1500 mmHg/s are considered as markers of depressed myocardial contractility [59].

2.2.4. Stroke Volume

Stroke volume is the amount of blood ejected by the heart in each beat and is the difference between end-diastolic volume and end-systolic volume. Stroke volume is affected by filling time (e.g. raise in stroke volume when duration of diastole is longer), the Frank-Starling mechanism (e.g. increased venous return produces stretching of sarcomeres that its translated into an increase in contractility because more myosin heads are in contact with actin's active

sites), sympathetic activation and release of catecholamines that increase contractility, and the vasomotor tone of blood vessels. The normal stroke volume range is ~50-120 ml at rest [54].

2.2.5. Cardiac Output

Cardiac output represents the amount of blood ejected by the ventricle per minute and is the product between heart rate and stroke volume. Cardiac output is constantly adjusted to maintain metabolic demands. On average, cardiac output is ~5 L/min at rest and during exercise this value can increase up to ~20-25 L/min [60].

2.2.6. Blood Pressure

Blood pressure is the hydrostatic force exerted by the blood on the wall of a vessel or a chamber of the heart. Systolic blood pressure (SBP) is the pressure generated by the blood on the wall of the vessel during the ventricular contraction. Diastolic blood pressure (DBP) is produced during ventricular relaxation. The difference between SBP and DBP is known as pulse pressure (PP). In a simplistic model represented by Ohm's Law, mean blood pressure can be expressed as the product between stroke volume, heart rate, and systemic vascular resistance. Blood pressure is determined by the interaction among many cardiovascular (e.g. cardiac output), renal (e.g. the renin-angiotensin-aldosterone system regulating sodium absorption and vasoconstriction), nervous (e.g. sympathetic/parasympathetic balance regulating vascular tone), and endocrine (e.g. catecholamines) factors and the vascular compliance [61].

2.2.7. Pulse Waves and Wave Reflections

Elastic central arteries, such as the aorta, are stretched during systole to accommodate the blood coming from the left ventricle. Due to the viscoelastic properties of elastic arteries, their wall recoils to maintain blood flow during diastole. In addition to this damping effect, a pressure wave is generated at the wall and then is transmitted through the arterial tree. The speed of propagation of pulse waves, also known as pulse wave velocity (PWV), depends on the characteristics of the vessel. For example, PWV is slower in elastic arteries in comparison to resistance vessels and is faster in the presence of arterial stiffness. Further, a portion of the transmitted forward pressure wave is reflected toward the ventricle at branches or at sites with more resistance (e.g. arterioles) and merges with a secondary forward pressure wave. Consequently, wave reflection amplifies SBP and the amount of amplification can be measured through pulse wave analysis (PWA) by the augmentation index (AIx). The AIx is the ratio between the augmented pressure and the pulse pressure. If the reflection wave overlays the forward wave at diastole it will favor coronary blood flow. Conversely, if the reflected wave is fast enough to overlay a forward wave during systole, it will increase afterload [54,58].

2.2.8. Blood Flow and Blood Flow Patterns

Blood flow refers to the movement of blood through a vessel or the heart and it is expressed in terms of volume as a function of time. Blood travels due to differences in pressure, from an arterial high-pressure end to a venous low-pressure end. The amount of blood flow is directly related to pressure differences and inversely related to the peripheral vascular resistance. The main variables that affect blood flow are cardiac output (e.g. an increase in stroke volume or heart rate raise blood flow), blood volume (e.g. hypovolemia decrease blood flow), blood viscosity (e.g.

polycythemia increases viscosity and produces resistance to the flow), compliance (e.g. arterial stiffness increases the resistance to blood flow), diameter (e.g. vasodilation increases blood flow), and length (e.g. larger vessels generate more resistance) of the vessel.

The cardiovascular system has two types of mechanisms to adjust blood flow. The first is the intrinsic control generated by metabolic regulation (e.g. chemoreceptors that sense the concentrations of oxygen, carbon, dioxide, adenosine, hydrogen, and potassium ions to adjust the diameter of the artery according to organ or tissue necessities), myogenic response (e.g. an increase in blood flow induce a vasoconstriction), and endothelial shear stress. The second is the extrinsic control provided by the autonomic nervous system (e.g. an increase in sympathetic activity produces vasoconstriction and blood flow reduction in most vessels), the endocrine system (e.g. catecholamines bind to α-adrenergic receptors of arterioles to enhance vascular resistance and reduction of blood flow), and the renin-angiotensin-aldosterone system (e.g. angiotensin II acts as a vasoconstrictor) [54].

The endothelium of arteries is constantly interacting with pulsatile blood flow. Blood flow intrinsically regulates vascular function and structure through cellular mechanotransduction pathways [62]. This control is dependent on blood flow singularities; specifically, its magnitude, directionality, and type [63,64]. Blood flow magnitude, also known as endothelial shear stress (ESS), can be defined in terms of the amplitude of the tangential force produced by the friction of the flowing blood on the endothelial apical surface and it can be categorized as low-ESS (<10 dynes/cm^2) or high-ESS (≥10 dynes/cm^2). Directionality can be described as anterograde if blood flows downstream, retrograde if blood flows upstream, or oscillatory if the flow is bidirectional [64]. Finally, blood flow is classified as laminar if blood travels in undisturbed streamlines or as turbulent if blood undergoes irregular fluctuations and chaotic velocity changes [65]. High-ESS

and laminar flow have shown to increase vascular NO bioavailability, and contrarily, low-ESS and turbulent flow independently impair endothelial NO production [66]. However, some studies have found that turbulent flow may be beneficial for vascular health. As an example, Gurovich and Braith [67] evaluated blood flow patterns created by enhanced external counterpulsation and its effects on femoral and brachial flow-mediated dilation (FMD) in 18 healthy young males. They found that enhanced external counterpulsation generated retrograde turbulent blood flow in the femoral artery and that this blood flow pattern improved femoral FMD. In addition, Gurovich and Braith [68] analyzed blood flow patterns in the brachial and femoral arteries during endurance and resistance exercise of 8 young healthy males and they described the presence of turbulence blood flow when workloads were at 40% or above their maximal exertional capacities during both types of exercises. The beneficial effects of exercise in vascular health are well established [21] and the fact that turbulent blood flow is developed during these conditions suggests that turbulence may also be favorable for the vasculature. Moreover, Cheng et al. [69] reported that disturbed blood flow offered plaque stability to atherosclerotic lesions in the carotid artery of an *in vivo* animal model, which could be considered as another example where turbulent blood flow may not be detrimental for the endothelium.

2.3. High Blood Pressure

2.3.1. Definition, Classification, and Epidemiology

High blood pressure is the most common cause of CVD (e.g. coronary heart disease, heart failure, stroke, myocardial infarction, atrial fibrillation, and peripheral artery disease), chronic kidney disease, and cognitive impairment [8]. Cardiovascular risk increases in a log-linear manner with blood pressure beginning from <115/75 mmHg to >180/105 mmHg [70]. The

operational definition of high blood pressure in adults is two or more office blood pressure measurements obtained on two or more visits that are >120 mmHg for SBP or ≥80 mmHg for DBP [7]. Even though there is no clear threshold level of blood pressure that defines when end-organ damage starts, an operational definition of high blood pressure is useful to simplify the diagnosis and guide the management of this condition [71]. Currently, high blood pressure is conceptually defined as the level of blood pressure at which there are more benefits of using an evidence-based treatment (e.g. lifestyle interventions, drugs) than risks [6]. Table 2 displays the most current classifications of high blood pressure published by the Seventh Joint National Committee (JNC 7) [72], the American College of Cardiology/American Heart (ACC/AHA) Association Task Force [7], and the European Society of Cardiology/European Society of Hypertension (ESC/ESH) [6].

Table 2. Blood Pressure Classification

SBP (mmHg)		DBP (mmHg)	JNC 7 (2003) [72]	ACC/AHA (2017) [7]	ESC/ESH (2018) [6]
<120	and	<80	Normal BP	Normal BP	Optimal BP
120-129	and	<80	Pre-HTA	Elevated BP	Normal BP
130-139	or	80-89	Pre-HTA	Stage 1 HTA	High normal BP
140-159	or	90-99	Stage 1 HTA	Stage 2 HTA	Grade 1 HTA
160-179	or	100-109	Stage 2 HTA	Stage 2 HTA	Grade 2 HTA
≥180	or	≥110	Stage 2 HTA	Stage 2 HTA	Grade 3 HTA

BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; HTA: hypertension.

The 2017 ACC/AHA guidelines reclassified high blood pressure categories into elevated blood pressure (SBP between 120-129 mmHg and DBP <80 mmHg), stage 1 hypertension (SBP between 130-139 mmHg or DBP between 80-89 mmHg), and stage 2 hypertension (SBP between ≥140 mmHg or DBP ≥90 mmHg) [7]. The first two categories proposed by the

ACC/AHA were previously defined by the JNC 7 as prehypertension. The use of the term prehypertension was intended to generate awareness among individuals with this range of blood pressure and to encourage health care professionals to promote healthy habits. Nonetheless, these goals were not accomplished, and less health care was provided [73]. The evidence behind the reduced blood pressure threshold to define hypertension by the ACC/AHA is based on nine longitudinal clinical studies in which major CVD events and the combination of fatal and nonfatal stroke were significantly lower when blood pressure was maintained below 130/80 mmHg [7]. However, as emphasized by The American College of Physicians and the American Academy of Family Physicians, no statistical benefit was found in CVD mortality when blood pressure was below 130/80 mmHg [74]. Despite the reduction on the threshold to define hypertension, the ACC/AHA guidelines still advocate for non-pharmacological interventions (e.g. exercise) as the primary treatment option for elevated blood pressure or stage 1 hypertension with an estimated 10-year risk of CVD of <10%. Overall, the ACC/AHA blood pressure classification allows early recognition of cardiovascular risk in individuals with high blood pressure and further management through lifestyle interventions [17].

The prevalence of high blood pressure is dependent on the blood pressure cut off values established to define hypertension. For example, according to the National Health and Nutrition Examination Survey (NHANES), if hypertension is defined according to the JNC 7 recommendations, approximately 34% of US adults (85.7 millions) have hypertension, meanwhile, if the ACC/AHA classification is taken into consideration, the prevalence of hypertension in US adults rises to 46% (116.0 million). High blood pressure has a great impact on the health care system with an estimated cost of $51.2 billion. Projected figures suggest that the cost will increase up to $200 billion by 2030 [1].

2.3.2. Etiology

High blood pressure is a multifaceted gene disorder exacerbated by environmental factors, including high-salt intake, physical inactivity, smoking, and alcohol consumption [7]. A total of 120 single-nucleotide polymorphisms associated with blood pressure homeostasis have been identified, but they only can explain ~3.5% of the trait variance [75]. Primary hypertension is defined as high blood pressure that cannot be explained by a secondary cause, like renal parenchymal disease, renovascular disease, primary aldosteronism, obstructive sleep apnea, pheochromocytoma, and Cushing's syndrome among others, representing 95% of all cases of high blood pressure. The remaining 5% of the cases are classified as secondary hypertension [71].

2.3.3. Pathophysiology

The development of high blood pressure in humans requires the malfunction of one or more factors involved with blood pressure control. According to the Mosaic Theory [22], there are common molecular mechanisms that govern the events occurring at both cellular and organ level in high blood pressure. Those mechanism will be described in the following sections.

2.3.3.1. Endothelial Dysfunction

Endothelial dysfunction is a pathological vascular state characterized by an unbalance between vasodilatory and vasoconstrictory mechanisms [76], and generally defined as the decrease in NO bioavailability within the endothelium [77]. Endothelial dysfunction is considered a central feature in high blood pressure pathology. High-salt intake promote water retention and subsequent blood pressure elevation. Healthy individuals can regulate blood

pressure after high-salt intake due to the continuous release of NO from the endothelium that produces vasodilation. When the endothelium is dysfunctional, blood pressure rises mainly because NO levels are significantly reduced and levels of potent vasoconstrictors (e.g. endothelin-1) are significantly elevated. Additionally, high-salt intake in susceptible individuals with high blood pressure is associated with an elevation of transforming growth factor-β that leads to fibrosis, oxidative stress, and reduction of NO. Moreover, endothelial dysfunction can be directly exacerbated by angiotensin II, aldosterone, and oxidative stress. Angiotensin II deteriorates endothelial function by direct vascular injury from oxidative stress and inflammatory pathways. Meanwhile, aldosterone has shown to promote endothelial dysfunction by increasing vascular smooth muscle cell proliferation, extracellular matrix deposition, collagen turnover, vascular fibrosis, and oxidative stress. Simultaneously, oxidative stress is known to affect endothelial function by converting NO into peroxynitrite [8].

2.3.3.2. Oxidative Stress

Reactive oxygen species (ROS) are oxygen metabolites such as superoxide (O_2^-) that can accept electrons from other molecules, donate electrons to other molecules, or react and combine with other molecules. In the case that nitrogen molecules such as NO are involved in redox reactions, they receive the denomination of reactive nitrogen species (RNS). To counterbalance ROS production, the body has several antioxidant pathways to buffer redox reactions. As an example, superoxide dismutase (SOD) converts $O2^-$ into water and hydrogen peroxide (H_2O_2), the latter molecule in turn is converted to oxygen and water by catalase [78].

Oxidative stress refers to a state of imbalance in which ROS and RNS production overcomes the antioxidant capacity of the body [79]. Major sources of vascular ROS are

nicotinamide adenine dinucleotide phosphate hydrogen oxidase (NOX), uncoupled eNOS, xanthine oxidase, and the mitochondria [80]. Related to high blood pressure, a vicious cycle is observed in vessels where O_2^- produced by NOX combines with NO, which is synthesized by eNOS, and forms peroxynitrite. Then, eNOS is destabilized by peroxynitrite and its unstable form produces more O_2^-. In addition, oxidative stress can lead to a deficit of eNOS cofactors tetrahydrobiopterin (BH4) and L-arginine. All these reactions promote a reduction in NO bioavailability [79]. Oxidative stress has been associated to high blood pressure in both animal[81] and human studies [82] and it appears to exacerbate several mechanisms involved with blood pressure regulation [8,78,83].

2.3.3.3. Inflammation

High blood pressure is known to be part of an inflammatory process [84-86]. This inflammatory process consists of complex interactions between inflammatory cells and the immune system [8]. An inflammatory state leads to increased expression of adhesion molecules in the vasculature and the release of inflammatory cytokines, chemokines, matrix metalloproteinases, and growth factors that promotes the thickening of the intima, vascular fibrosis, degradation of extracellular matrix, and end-organ infiltration by immune cells [8,83,84]. Levels of inflammatory cytokines such as IL-6 and TNF-α are elevated in individuals with high blood pressure in comparison to normotensive individuals [85-89]. For its part, CRP has been employed as a biomarker for systemic inflammation in CVD and its levels have been positively correlated to SBP and end-organ damage in individuals with high blood pressure [90].

2.3.3.4. Autonomic Dysfunction

The autonomic nervous system regulates blood pressure through a balance between sympathetic and parasympathetic activity. When blood pressure rises, baroreceptors located in the carotid sinus and aortic arch sense the arterial stretching and send a message to the brain to reduce sympathetic outflow impulses which in turn reduces blood pressure [8]. The sympathetic nervous system is more active in individuals with high blood pressure [91] and that this increased activity induces α-1 adrenergic receptor-mediated endothelial dysfunction, vasoconstriction, release of renin, vascular smooth muscle proliferation, and arterial stiffness [92].

2.3.3.5. The Renin–Angiotensin–Aldosterone System

The renin-angiotensin-aldosterone system is critical in the maintenance of blood pressure. Renin is an enzyme synthesized by juxtaglomerular cells that is released into the bloodstream in response to a reduction in renal afferent arteriolar perfusion pressure, a reduction in sodium levels, renal sympathetic nerves activation, or under the presence of vasodilators (e.g. prostaglandin E2). Renin hydrolyzes angiotensinogen secreted from the liver into angiotensin I that is then converted into angiotensin II by the angiotensin-converting enzyme. Angiotensin II is known to bind the type 1 angiotensin II receptor which triggers arteriolar vasoconstriction, sympathetic hyperactivity, sodium reabsorption, fluid retention, and the release of anti-diuretic hormone and aldosterone. Aldosterone is also involved with water and sodium reabsorption [8,93]. Individuals with high blood pressure have elevated plasma levels of renin and angiotensin II [94] and the first phase for high blood pressure development is likely due to renal

vasoconstriction induced by hyperactivation of both the sympathetic and the renin-angiotensin-aldosterone systems [83].

2.3.3.6. Natriuretic Peptides Deficiency

Natriuretic peptides, such as atrial natriuretic peptide and brain natriuretic peptide, are released by the atrium and ventricle after a stretch signal secondary to blood volume expansion due to sodium intake. Both peptides reduce blood pressure by inducing vasodilation, shifting fluid to the interstitial space, increasing glomerular filtration, and reducing sodium reabsorption. Natriuretic peptide deficiency is another factor that favors high blood pressure [8].

2.3.3.7. Arterial Stiffness

Arterial stiffness can be defined as the rigidity of arterial walls and reflects the fragmentation and loss of elastin with the overproduction and accumulation of collagen, mainly at the media layer, but some experiments have shown that the adventitia layer is also involved. Arterial compliance is determined by the ratio between elastin and collagen and is inversely proportional to arterial stiffness. Aging and high blood pressure are associated with a decreased ratio of elastin/collagen. Increased intraluminal pressure due to high blood pressure stimulates collagen production to compensate for microfractures of elastin fibers. Additionally, matrix metalloproteinases produced by inflammatory pathways intensify elastin degradation and collagen deposition. Elastic arteries are the main vessels to be affected by arterial stiffness while resistance vessels are usually not compromised. Endothelial dysfunction, angiotensin II, aldosterone, and oxidative stress stimulate vascular hypertrophy and matrix remodeling, favoring arterial stiffness [26,95]. Likewise, arterial stiffness increases afterload, reduces cardiac

perfusion during diastole, and increases PP. The latter can be a determinant for end-organ microvascular damage due to the rise of blood flow [96].

2.3.4. Cardiovascular Risk Factors and Quality of Life

A cardiovascular risk factor refers to a measurable variable associated to the presence of CVD and at the same time is an independent risk predictor for the development of CVD [97]. The most common risk factor for CVD is peripheral high blood pressure [1]. SBP, DBP, and PP have independently been associated to CVD [7]. High blood pressure accounts for approximately 10 million deaths and 200 million disability-adjusted life years worldwide. SBP ≥ 140 mmHg explains around 70% of the mortality and disability burden [6]. Individuals with elevated blood pressure or stage 1 hypertension have a greater chance to progress to stage 2 hypertension and to develop CVD and chronic kidney disease in comparison to normotensive individuals [1]. Additionally, high blood pressure is commonly associated to other cardiovascular risk factors, such as central blood pressure, cardiorespiratory fitness, arterial stiffness, dyslipidemia, and obesity.

Central blood pressure reflects the pressure at the aortic wall and has shown to be more strongly related to future cardiovascular events than traditional brachial blood pressure [98]. As an example, central systolic blood pressure (cSBP) and central pulse pressure (cPP), rather than brachial pressures, were independently associated with cardiovascular mortality and events in 2,403 American Indians in a follow-up study with a mean duration of 4.8 years [99].

Cardiorespiratory fitness refers to the ability of the cardiovascular system to supply oxygen for muscle contraction during physical activity. Maximal oxygen uptake (VO_2max) is the maximum rate of oxygen consumption measured during an incremental cardiopulmonary test

and reflects the integrity of the cardiovascular system. VO_2max is an independent predictor of CVD mortality [100,101].

Arterial stiffness, besides being part of the physiopathology of high blood pressure, is an independent predictor of all-related cardiovascular causes of mortality, coronary morbidity, and fatal stroke in individuals with high blood pressure. The reference standard technique to assess arterial stiffness is PWV [102].

Dyslipidemia refers to a disruption of the lipid metabolism and is reflected by plasma elevations of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), very low-density lipoprotein cholesterol (VLDL-C), or triglycerides (TG) or a reduction of high-density lipoprotein cholesterol (HDL-C) [103]. Each parameter of the lipid profile has been shown to be a strong independent predictor for CDV [104]. Dyslipidemia is a risk factor for atherosclerosis and it has been reported that lower levels of LDL-C and TC are associated to better health outcomes [105].

Obesity is an abnormal accumulation of body fat which increases the risk for CDV. BMI is the most common assessment to define obesity and involves the ratio between weight and the square of height [106,107]. However, BMI misclassifies cardiometabolic health [108] and doesn't consider body fat distribution (e.g. visceral type) [109]. Current approaches advocate for the use of body composition as an assessment tool to determine obesity [110].

Finally, quality of life refers to the subjective evaluation of the bio-psycho-social wellness of an individual and includes aspects related to physical and mental health, relationships with the community, workplace, friends, family, and personal goals [111]. Several studies have reported that individuals with high blood pressure tend to have significantly worse scores in surveys related to quality of life in comparison to normotensive individuals [112-115].

2.4. Physical Activity and Exercise

2.4.1. Definitions and Epidemiology

Physical activity refers to any type of body movement originated by skeletal muscle contractions that results in energy expenditure [116] categorized in leisure-time physical activity or occupational physical activity. Leisure-time physical activity comprises those activities that happen during spare time and are based on personal interest or needs (e.g., sports participation, exercise training programs, playing music, walking, hiking, etc.), while occupational physical activity covers those activities that are developed during a typical 8- to 12-hour work shift [117].

Exercise is a subtype of leisure-time physical activity that is planned, structured, and repetitive, which's goal is to improve or maintain one or more features of physical fitness (e.g., cardiorespiratory endurance, muscle endurance, muscle strength, muscle power, flexibility, agility, balance, agility, and body composition) [117,118]. From a mechanistic point of view, exercise can be described as dynamic or static. Dynamic exercise, also known as isotonic, allows movement of the arms, legs, or trunk in a concentric or eccentric pattern. Static or isometric exercise generates muscle contraction without movement of the limbs or trunk [119]. At the same time, exercise can be described according to the metabolic contribution from the phosphagen, glycolytic, and oxidative phosphorylation energy pathways for muscle contraction. Current efforts have been made to abolish the terms "aerobic" and "anaerobic" exercise because they misrepresent the connections among the energy pathways involved with the physiology of muscle contraction [120]. For example, lactate is a metabolic product of glycolysis that doesn't require oxygen for its production. Once it is formed, lactate can be transported inside the mitochondria and it can be used as a fuel source by the oxygen-dependent oxidative phosphorylation pathway [121]. Also, all three energy pathways operate simultaneously during

exercise but one of them predominates over the other two depending on the intensity and duration of the exercise bout [122,123].

A physically inactive adult is defined as someone that covers less than 150 minutes of moderate-to-vigorous physical activity per week or less than 75 minutes of vigorous physical activity per week [124,125]. Physical inactivity is considered the fourth cause of death worldwide [126] and represents a major risk factor for CVD. Estimates suggests that only 21.6% of US adults met the criteria for minimal physical activity recommendations. Translating this into economical costs, physical inactivity represents 1.5% to 3.0% of total direct healthcare expenditures [1]. For every dollar invested to increase physical activity in the community, there is a savings of three to six dollars in healthcare [1,19]. Similarly, this trend is also observed in CVD individuals who follow cardiovascular rehabilitation programs. Long-term retention rates ranges from 21% to 50% [35-37]. Multiple factors affect the decision to drop out from an exercise program such as personality, intrinsic motivation, personal preferences to exercise, and organizational characteristics [38-42]. The incorporation of more exercise alternatives to the traditional physical activity programs (e.g. walking, running, cycling, and resistance training) might avoid the large dropout from cardiovascular rehabilitation programs and attract more people to start exercising [35,43,44]. Nonetheless, before a nontraditional modality of exercise can be recommended for health-related conditions and incorporated into cardiac rehabilitation programs, a solid scientific background must exist [45].

2.4.2. Exercise Prescription in Cardiovascular Diseases

Exercise prescription in CVD commonly refers to an individualized fitness program designed by a healthcare professional that seeks to: (1) prevent or treat a cardiovascular

condition, (2) improve cardiovascular risk factors (e.g., blood pressure, glycemia, lipid profile, central adiposity, physical inactivity, and sedentary behavior), and (3) boost one or more components of physical fitness like cardiorespiratory endurance, muscular strength, muscular power, muscular endurance, flexibility, balance, body composition, agility, coordination, or balance [127,128].

The basic principles to prescribe exercise are: (1) modality, (2) intensity, (3) duration, (4) frequency, and (5) progression[127].

Modality refers to the type of activity that will be performed. The most common exercise modalities selected to explore exercise-induced effects on the cardiovascular system are walking, running, cycling, and resistance training [18,30,129-137]. Cardiovascular adaptations are modality-dependent [21,138]. For example, Pelliccia et al. [139] described that endurance sports are associated with a higher left ventricle mass in comparison to strength sports. Additionally, Boraita et al. [140] showed that although the aortic root size of 3,1281 elite athletes was within the normal range for the general population, elite athletes participating in endurance sports had larger aortic dimensions in comparison to those elite athletes from strength-focus disciplines. Nonetheless, these cross-sectional studies have the limitation of introducing bias due to the inter-subject variability. To solve the inherent limitations of cross-sectional studies, Spence et al. [141] designed a prospective randomized longitudinal study to evaluate the impact of different exercise modalities in the vasculature. They found that upper-body resistance training increased the resting diameter and the function of the brachial artery but these characteristics remained unchanged in the femoral artery, while lower-body endurance training only improved the structure and the functionality of the femoral artery. No changes were observed in the resting diameter and the function of the brachial artery. Moreover, metabolic responses to exercise are

also dependent on the modality. Dufour et al. [142] and Peñailillo et al. [143] reported that HR, blood lactate, and VO_2 were significantly lower in eccentric cycling compared to concentric cycling.

Intensity is the degree of effort employed during exercise that can be expressed as absolute intensity (total rate of energy expenditure for a specific activity) or relative intensity (percentages of an absolute value). Absolute intensity parameters include oxygen uptake (L/min), oxygen uptake normalized to body mass (ml/kg/min), energy (kcal/min), and multiples of the resting metabolic rate (METs). Relative intensity can be described as a percentage of maximal oxygen uptake (VO_2max), oxygen uptake reserve (VO_2R), peak oxygen uptake (VO_2peak), maximal heart rate (HR_{max}), heart rate reserve (HRR), and one-repetition maximum (1-RM) for resistance training [117]. Other alternatives to quantify intensity are the classification of the exertion according to ventilatory thresholds, lactate threshold, and Borg's Rating of Perceived Exertion (RPE). Few studies have determined the cardiovascular adaptations to different exercise intensities. Goto et el. [144] evaluated the effects of 12-weeks of cycling at three different intensities (25% VO_2max, 50% VO_2max, and 75% VO_2max) on the endothelium-dependent vasodilatory response. They found that only moderate-intensity exercise (50% VO_2max) increased the endothelium-dependent vasodilatory response while high-intensity increased plasma levels of oxidative stress. In contrast, Rakobowchuk et al. [145] described similar improvements in arterial stiffness after six weeks of sprint interval training (six 30-second "all-out" cycling, 4.5-minute of active recovery between each bout, three days per week) and endurance training (40-60 minutes of cycling at 65% VO_2peak, five days per week). A meta-analysis [136] comparing the effects of HIIT and moderate-intensity continuous training on vascular function favored HIIT.

Duration is defined as the amount of time expended during exercise and can be performed continuously or intermittently. For the specific case of resistance training, volume (number of sets and repetitions per exercise) is used instead of duration. Depending on the amount of intensity and duration, exercise protocols can range from moderate-intensity continuous training to high-intensity interval training (HIIT). For example, continuous exercise can be applied at low- and moderate-intensity during an extended period (e.g. 60 min) while HIIT is based on intervals of maximal effort for a short period (e.g. 30 seconds to 4 minutes) interspersed by recovery time at low-intensity. Polarized training is comprised of an exercise session where 70-80% of the time is performed at low-intensity (just below lactate threshold or first ventilatory threshold) and the remaining 20-30% of the time is performed using HIIT. Data suggest that polarized training might be more beneficial for cardiovascular health than moderate-intensity continuous exercise or HIIT alone [146].

Frequency pertains to the number of times that an exercise session is carried out during certain period (e.g. 3 times per week, 2 times per day). Most studies employing exercise training as an intervention have shown benefits for health when the frequency is at least 3 to 5 sessions per week [147].

Progression refers to the periodical adjustment of any of the previous variables that will be dependent on the individual's training responses and the exercise programs objectives [127].

2.4.3. Boxing Training

Boxing training is a nontraditional exercise modality characterized by stand-up punching, coordinated body movements, balance, and agility that requires high levels of endurance, strength, and technical skills. A boxing training session can include several types of drills like

shadowing, sparring, heavy bag punching, speed bag, mitt work, skipping, jumping the rope, footwork, running, technique development, and core exercises. A current popular approach among fitness centers is the use of non-contact boxing classes which include all the activities of boxing training, except for sparring. Usually, a workout is divided into rounds of two to three minutes of exercise at high-intensity followed by a resting period of one minute [46,48,148-150]. It has been described that boxing training elicits a great metabolic response. For example, Ghosh [150] showed that amateurs young boxers evoked high metabolic responses during a boxing round with mean peaks of VO_2, HR, and lactate of ~58 ml/kg/min, 192 bpm, and 13.6 mmol/L, respectively.

Very few studies have employed boxing training as an intervention to improve health in CVD. In a case report, Shultz et al. [53] evaluated the impact in cardiometabolic variables of a 12-week program that combined 30-minute boxing training and 30-minute resistance training three times per week in three obese male adolescents. The boxing program included shadow boxing, heavy bag punching, and mitt punching at an intensity of 90% HR_{max}. The resistance protocol consisted of at least six exercises of major muscle groups at 70-90% HR_{max}. The authors described a reduction in visceral fat thickness and carotid β-stiffness index and improvements in VO_2max and AIx. In another study, Cheema et al. [52] recruited twelve adults with abdominal obesity for a 12-week pilot randomized parallel pilot trial to assess the effectiveness of boxing training in obesity, cardiovascular outcomes, and quality of life in comparison to walking. The boxing group (n = 6) underwent 50 minutes of boxing training four times per week that included a 5-minute warm up of skipping followed by three series of five rounds for each of the following: heavy bag punching, focus mitts, circular body bag, footwork, and skipping. Each round was composed by two-minute high-intensity exercise at 86-89% HR_{max} followed by one-

minute of rest. Meanwhile, the control group (n = 6) completed 50 minutes of unsupervised continuous brisk walking at 64-77% HR_{max}, four times per week. In the boxing group, they found a statistically significant post-intervention reduction in percent body fat (%BF), brachial blood pressure, and AIx with improvements in both VO_2max and quality of life. Similarly, Yli-Piipari et al. [151] evaluated the effects of boxing training in conjunction with a 12-week lifestyle program on cardiometabolic and psychological outcomes in Hispanic children and adolescents. A total of 22 children and adolescents with a BMI above the 85th percentile for their age were recruited for a case series study where they underwent one-hour of boxing training twice per week, one-hour nutritional education once per week, group meetings for behavior modifications, and one meeting with a pediatrician to reinforce the motivation. This program showed a statistically significant reductions in waist circumference, BMI, and glycemic control along with significant improvements in intrinsic motivation and introjected regulation. Lastly, Park et al. [49] evaluated the effects of boxing training on upper limb function, balance, gait, and quality of life in 30 stroke patients. Randomly dividing the sample into two groups, the first group (boxing, n = 15) underwent 30 minutes of boxing training (5-minute warming up, 10-minute mitt punching, 10-minute heavy bag punching, and 5-minute cooling down) followed by 30 minutes of physical therapy, 3 times a week for 6 weeks. The second group (control, n = 15) only performed 30 minutes of physical therapy 3 times a week for 6 weeks. During the first 2 weeks, the boxing sessions were in a sitting position, then evolved to an alternation of sitting and standing for the following 4 weeks. They showed that boxing training significantly improved the functionality of the upper limb, the dynamic component of balance, the walking ability, and quality of life. Additionally, boxing training has been applied as a complementary therapy in

Parkinson's disease where patients have shown promising results regarding their clinical evolution [50,152].

2.4.4. Exercise Effects on the Cardiovascular System in Individuals with High Blood Pressure

2.4.4.1. Peripheral Blood Pressure

Comprehensive meta-analyses have shown that exercise significantly reduces brachial blood pressure and can be employed as an effective treatment intervention in individuals with high blood pressure [18,28,29]. Cornelissen et al. [18] described an overall reduction in SBP/DBP of 3.5/2.5, 1.8/3.2, and 10.9/6.2 mmHg in endurance, resistance, and isometric training, respectively. According to their results, at least 30 minutes of moderate- or high-intensity exercise training were required to reduce blood pressure. No difference in blood pressure was observed between exercise frequencies (e.g., 3, 4, or >4 times per week). Similarly, de Sousa et al. [28] found reductions of 8.2/4.1 mmHg in a meta-analysis that involved resistance training as a single intervention in individuals with high blood pressure. Meanwhile, Inder et al. [29] in another meta-analysis depicted 5.2/3.9 mmHg reductions after isometric exercise training in healthy and individuals with high blood pressure. Table 3 describes protocols and outcomes of randomized trials involving exercise training in individuals with high blood pressure.

Table 3. Characteristics of previous studies that evaluated the effects of exercise on systolic and diastolic blood pressure in individuals with high blood pressure.

Author	*Year*	*Design*	*N*	*Modality*	*Frequency*	*Intensity*	*Duration*	*Period*	*Outcome*
Duncan et al. [153]	1985	RCT	56	Walking Jogging	3 d/wk	75% HR_{peak}	60 min/d	16 wks	SBP ↓ 12 mmHg DBP↓ 7 mmHg
Hagberg et al. [154]	1989	RCT	30	Walking Jogging Cycling	3 d/wk	Low: 53% VO_2max Mod: 73% VO_2max	51 min/d	37 wks	Low: SBP ↓ 6 mmHg DBP↓ 9 mmHg Moderate: SBP ↓ 7 mmHg DBP↓ 3 mmHg
Tanabe et al. [155]	1989	RCT	31	Cycling	3 d/wk	40-60% VO2peak	60 min/d	10 wks	SBP ↓ 15 mmHg DBP↓ 7 mmHg
Martin et al. [156]	1990	RCT	27	Walking Jogging Cycling	4 d/wk	65-80% HRpeak	30 min/d	10 wks	SBP ↓ 6 mmHg DBP↓ 10 mmHg
Braith et el. [157]	1994	RCT	44	Mod: Walking High: Uphill Walking	3 d/wk	Mod: 70% HRR High: 85% HRR	45 min/d	26 wks	Mod: SBP ↓ 9 mmHg DBP↓ 8 mmHg High: SBP ↓ 8 mmHg DBP↓ 7 mmHg
Anderssen et al. [158]	1995	RCT	90	Walking Jogging	3 d/wk	60-80% HRpeak	60 min/d	52 wks	SBP ↓ 5 mmHg DBP↓ 5 mmHg
Kokkinos et al. [159]	1995	RCT	46	Cycling	3 d/wk	74% HRmax	44 min/d	16 wks	SBP ↓ 7 mmHg DBP↓ 5 mmHg
Ready et al. [160]	1996	RCT	53	Walking	3 d/wk 5 d/wk	60% VO_2max	60 min/d	24 wks	3 d/wk: SBP ↓ 7 mmHg DBP↓ 3 mmHg 5 d/wk: SBP ↓ 5 mmHg DBP↑ 1 mmHg
Tanaka et al. [161]	1997	RCT	18	Swimming	3 d/wk	60% VO_2peak	45 min/d	10 wks	SBP ↓ 6 mmHg DBP↓ 2 mmHg
Jessup et al. [162]	1998	RCT	21	Walking Stair climbing	3 d/wk	85% HR_{peak}	45 min/d	16 wks	24-hr ABPM: SBP ↓ 8 mmHg DBP↓ 4 mmHg
Murphy et al. [163]	1998	RCT	34	Brisk Walking	5 d/wk 7 d/wk	70-80 HR_{peak}	5 d/wk: 60 min/d 7 d/wk: 3 x 10min/d	10 wks	5 d/wk: SBP ↓ 5 mmHg 7 d/wk: SBP ↓ 7 mmHg
Sakai et al. [164]	1998	RCT	29	Cycling	3 d/wk	40-60% VO_2peak	60 min/d	4 wks	SBP ↓ 9 mmHg DBP↓ 7 mmHg
Hamdorf et al. [165]	1999	RCT	38	Walking	2 d/wk	40% HRR	25 min/d	26 wks	SBP ↑ 8 mmHg DBP↑ 3 mmHg
Higashi et al. [166]	1999	RCT	27	Walking Jogging	5-7 d/wk	52% VO_2peak	30 min/d	12 wks	SBP ↓ 8 mmHg DBP↓ 4 mmHg
Higashi et al. [167]	1999	RCT	17	Walking Jogging	5-7 d/wk	52% VO_2peak	30 min/d	12 wks	SBP ↓ 7 mmHg DBP↓ 4 mmHg
Georgides et al. [168]	2000	RCT	55	Walking Cycling	3-4 d/wk	70-85% HRR	45 min/d	26 wks	SBP ↓ 3 mmHg DBP↓ 5 mmHg
Hass et al. [169]	2001	RCT	26	Recumbent Step training	3 d/wk	75% HRR	40 min/d	12 wks	SBP ↓ 3 mmHg DBP↓ 7 mmHg
Moreu et al. [170]	2001	RCT	24	Walking	7 d/wk		9700 steps/day	24 wks	SBP ↓ 11 mmHg DBP ↔
Staffileno et al. [171]	2001	RCT	18	Walking Cycling	5 d/wk	50-60% HRR	3 x 10 min/day	8 wks	SBP ↓ 7 mmHg DBP↓ 4 mmHg
Tsai et al. [172]	2002	RCT	42	Walking Jogging	3 d/wk	60-70% HR_{peak}	30 min/d	12 wks	SBP ↓ 11 mmHg DBP↓ 5 mmHg
Tsai et al. [173]	2002	RCT	23	Walking Jogging	3 d/wk	60-70% HR_{peak}	30 min/d	12 wks	SBP ↓ 18 mmHg DBP↓ 10 mmHg
Asikainen et al. [174]	2003	RCT	130	Walking	5 d/wk	65% VO_2peak	300 kcal/d	15 wks	SBP ↑ 4 mmHg DBP↓ 1 mmHg
Jessup et al. [175]	2003	RCT	30	Walking Cycling Stair climbing	2 d/wk	75% HR_{peak}	45 min/d	16 wks	SBP ↓ 10 mmHg DBP↓ 6 mmHg
Tsuda et al. [176]	2003	RCT	16	Walking Jogging Calisthenics	2 d/wk	AT	50 min/d	26 wks	SBP ↓ 10 mmHg DBP↓ 6 mmHg
Santa-Clara et al. [177]	2003	RCT	60	Walking Cycling Rowing	3-4 d/wk	70-85% HR_{peak}	45-60 min/d	26 wks	SBP ↔ DBP↓ 4 mmHg
Maeda et al. [178]	2004	RCT	15	Cycling	5 d/wk	80% VT	30 min/d	12 wks	SBP ↓ 12 mmHg DBP↓ 7 mmHg
Tsai et al. [179]	2004	RCT	102	Walking Jogging	3 d/wk	60-70% HR_{peak}	30 min/d	10 wks	SBP ↓ 13 mmHg DBP↓ 6 mmHg

Table 3. cont.

Murtagh et al. [180]	2005	RCT	49	Bisk walking	3 d/wk	73% HR_{peak}	20 min/d	12 wks	SBP ↔ DBP ↔
Tully et al. [181]	2005	RCT	26	Bisk walking	5 d/wk	"slightly breathless"	30 min/d	12 wks	SBP ↓ 12 mmHg DBP↓ 4 mmHg
Church et al. [182]	2007	RCT	464	Walking Jogging Cycling	3 d/wk	50% VO_2peak	28 min/d 49 min/d 62 min/d	26 wks	28 min/d: SBP ↔ DBP ↔ 49 min/d: SBP ↓ 1 mmHg DBP ↔ 62 min/d: SBP ↓ 3 mmHg DBP ↔
Tully et al. [183]	2007	RCT	93	Walking	3 d/wk 5 d/wk	"slightly breathless"	30 min/d	12 wks	3 d/wk: SBP ↓ 6 mmHg DBP ↔ 5 d/wk: SBP ↓ 6 mmHg DBP↓ 3 mmHg
Brixius et al. [184]	2008	RCT	21	Running Cycling	3 d/wk	Lactate 3 mmol/L	60-90 min/day	24 wks	Running: SBP ↔ DBP ↔ Cycling: SBP ↓ 12 mmHg DBP↓ 6 mmHg
Westhoff et al. [185]	2008	RCT	24	Upper-limb cycling	3 d/wk	Lactate 2 mmol/L	30 min/day	12 wks	SBP ↓ 7 mmHg DBP↓ 6 mmHg
Krustrup et al. [186]	2009	RCT	32	Soccer Running	2-3 d/wk	82% HR_{peak}	60 min/day	12 wks	Soccer: SBP ↓ 8 mmHg DBP↓ 5 mmHg Running: SBP ↓ 8 mmHg DBP↓ 5 mmHg
Dalleck et al. [187]	2009	RCT	26	Walking	5 d/wk	50% VO_2R	30 min/day 45 min/day	12 wks	30 min/d: SBP ↓ 2 mmHg DBP↓ 2 mmHg 45 min/d: SBP ↓ 5 mmHg DBP↓ 2 mmHg
Hua et al. [188]	2009	RCT	40	Walking	4 d/wk	35-40% HRR	4.8 km/day	12 wks	SBP ↓ 11 mmHg DBP↓ 5 mmHg
Lamina et al. [189]	2010	RCT	357	Cycling	3 d/wk	60-79% HR_{peak}	60 min/day	8 wks	SBP ↓ 15 mmHg DBP↓ 4 mmHg
Saremi et al. [190]	2010	RCT	18	Walking Running	5 d/wk	80-85% HR_{peak}	50-60 min/day	12 wks	SBP ↓ 2 mmHg DBP↓ 2 mmHg
Pitsavos et al. [191]	2011	RCT	40	Cycling	3 d/wk	60-80% HR_{peak}	44 min/day	16 wks	SBP ↓ 12 mmHg DBP↓ 7 mmHg
Molmen-Hansen et al. [192]	2011	RCT	88	Walking Running uphill	3 d/wk	Mod: 70% HR_{max} HIIT: 4 x 4 min 90-95% HRmax, 3 min rest	Mod: 47 min/day HIIT: 38 min/day	12 wks	Mod: SBP ↓ 5 mmHg DBP↓ 4 mmHg HIIT: SBP ↓ 12 mmHg DBP↓ 8 mmHg
Izadi et al. [193]	2018	RCT	30	Cycling	3 d/wk	HIIT: 10 x 1.5 min 85-90% HRR, 2 min 50-55% HRR	35 min	6 wk	SBP ↓ 3 mmHg DBP↓ 2 mmHg
Harris et al. [194]	1987	RCT	26	Resistance	3 d/wk	40% 1RM	10 types 3 sets 20-25 reps	9 wks	SBP ↓ 5 mmHg DBP↓ 1 mmHg
Van Hoof et al. [195]	1996	RCT	19	Resistance	3 d/wk	70-90% 1RM	6 types 3 sets 10 reps	16 wks	SBP ↓ 4 mmHg DBP↓ 5 mmHg
Tsutsumi et al. [196]	1997	RCT	41	Resistance	3 d/wk	High: 75-85% 1RM Low: 55-65% 1RM	11 types 2 sets High: 8-12 reps Low: 12-16 reps	12 wks	High: SBP ↓ 6 mmHg DBP ↔ Low: SBP ↓ 13 mmHg DBP↓ 2 mmHg
Vincent et al. [197]	2003	RCT	62	Resistance	3 d/wk	High: 80% 1RM Low: 50% 1RM	13 types 1 set High: 8 reps Low: 13 reps	24 wks	High: SBP ↓ 3 mmHg DBP ↓ 2 mmHg Low: SBP ↔ DBP↔
Colado et al. [198]	2009	RCT	31	Resistance	3 d/wk	Elastic bands	8-16 types 2 sets 15-30 reps	24 wks	DBP↓ 5 mmHg

Table 3. cont.

Lovell et al. [199]	2009	RCT	24	Resistance	3 d/wk	70-90% 1RM	Incline squat 3 sets 6-10 reps	16 wks	SBP ↔ DBP↔
Laterza et al. [200]	2007	RCT	20	Cycling + Resistance	3 d/wk	Cycling: Resistance 70% VO_2peak	Cycling: 40 min Resistance: 10 min of sit-ups, push-ups, pull-ups	16 wks	SBP ↓ 15 mmHg DBP↓ 10 mmHg
Guimaraes et al. [201]	2010	RCT	56	Running + Resistance	3 d/wk	Continuous: 60% HRR HIIT: 50% HRR/80% HRR	40 min endurance + 20 min resistance	16 wks	SBP ↔ DBP↔
Figueroa et al. [202]	2011	RCT	24	Walking + Resistance	3 d/wk	60% HRmax	20 min endurance + 20 min resistance	12 wks	SBP ↓ 6 mmHg DBP↓ 5 mmHg
Okhubo et al. [203]	2001	RCT	39	Cycling + Resistance	2-3 d/wk	60% HRR Elastic bands	25 min endurance + 5 types	25 wks	SBP ↓ 5 mmHg DBP↓ 4 mmHg
Wiley et al. [204]	1992	RCT	15	Isometric	3 d/wk	30% MVC	4 series 2 min/ 3 min rest	8 wks	SBP ↓ 13 mmHg DBP↓ 15 mmHg
Taylor et al. [205]	2003	RCT	17	Isometric	3 d/wk	30% MVC	4 series 2 min/ 1 min rest	10 wks	SBP ↓ 19 mmHg DBP↓ 7 mmHg
Badrov et al. [206]	2013	RCT	24	Isometric	3 d/wk	30% MVC	4 series 2 min/ 1 min rest	10 wks	SBP ↓ 8 mmHg DBP↓ 5 mmHg
Blumenthal et al. [207]	1991	RCT	92	Resistance Endurance	2-3 d/wk	70% VO_2peak	30 min resistance, 50 min endurance	16 wks	Resistance: SBP ↓ 7 mmHg DBP↓ 6 mmHg Endurance: SBP ↓ 8 mmHg DBP↓ 6 mmHg
Cononie et al. [208]	1991	RCT	49	Resistance Endurance	3 d/wk	Resistance: 8-12 RM Endurance: 75-85% VO_2peak	Resistance: 10 types 1 set 12 reps Endurance: 35-45 min	26 wks	Resistance: SBP ↔ DBP↔ Endurance: SBP ↓ 8 mmHg DBP↓ 9 mmHg
Kraemer et al. [209]	2001	RCT	35	Endurance Resistance	3 d/wk	80-90% HRpeak	Endurance: 40 min Resistance: 25 min	12 wks	Endurance: SBP ↔ DBP↓ 6 mmHg Resistance: SBP ↔ DBP↓ 7 mmHg
Wood et al. [210]	2001	RCT	36	Endurance Resistance Combination	3 d/wk	Endurance: 60-70% HRR Resistance: 8-12 RM	Endurance: 45 min Resistance: 8 types 2 sets 8-12 reps	12 wks	Endurance: SBP ↓ 10 mmHg DBP↓ 3 mmHg Resistance: SBP ↔ DBP↔ Combination: SBP ↔ DBP↔
Sarsan et al. [211]	2006	RCT	60	Endurance Resistance	3-5 d/wk	Endurance: 50-85% HRR Resistance: 75-80% 1RM	Endurance: 30-45 min Resistance: 6 types 3 sets 10 reps	12 wks	Endurance: SBP↓ 10 mmHg DBP↓ 7 mmHg Resistance: SBP↓ 6 mmHg DBP↓ 8 mmHg
Simons et al. [212]	2006	RCT	59	Walking Resistance	2 d/wk	75% 1RM	Resistance: 6 types 1 set 10 reps	16 wks	Walking: SBP↓ 5 mmHg DBP↔ Resistance: SBP↓ 9 mmHg DBP↔
Collier et al. [213]	2008	PRT	30	Running Resistance	3 d/wk	Running: 65% VO_2peak	Running: 30 min Resistance: 9 types 3 sets 10 reps	4 wks	Running: SBP↓ 5 mmHg DBP↓ 3 mmHg Resistance: SBP↓ 4 mmHg DBP↓ 4 mmHg

Table 3. cont.

Silampää et al. [214]	2009	RCT	62	Cycling Resistance Combination	2 d/wk	Cycling: above AT Resistance: 10RM	Cycling: 60-90 min Resistance: 7-8 types 3-4 sets 6-8 reps	21 wks	Cycling: SBP ↔ DBP↔ Resistance: SBP↓ 7 mmHg DBP↔ Combination: SBP ↔ DBP↓ 4 mmHg
Beck et al. [215]	2013	RCT	43	Running Resistance	3 d/wk	Running: 65-85% HRmax Resistance: volitional fatigue	Running: 60 min Resistance: 7 types 2 sets 8-12 reps	8 wks	Running: SBP↓ 12 mmHg DBP↓ 3 mmHg Resistance: SBP↓ 10 mmHg DBP↓ 7 mmHg
Cheema et al. [52]	2015	PRT	12	Walking Boxing	4 d/wk	Walking: 64-77% HRmax Boxing: 2 min 86-89% HRmax, 1 min rest	50 min/d	12 wks	Walking: SBP ↔ DBP↔ Boxing: SBP↓ 14 mmHg DBP↓ 7 mmHg

Note. RCT: randomized controlled trial; PRT: parallel randomized trial

2.4.4.2. Central Blood Pressure

In a recent meta-analysis that included 38 randomized controlled trials, Zhang et al. [30] reported the effects of different exercise modalities on central blood pressure features such as high blood pressure, coronary artery disease, heart failure, and stroke in 2,089 individuals with CVD. They found that endurance training reduced cSBP, whereas resistance training reduced cSBP and cDBP and combined exercise reduced cSBP, cDBP, and AIx. In a subgroup analysis focused only in individuals with high blood performing endurance exercise, only cSBP showed a significant reduction.

2.4.4.3. Cardiorespiratory Fitness

Longitudinal studies have shown an inverse association between increased cardiorespiratory fitness and SBP [216-218]. Meanwhile, a meta-analysis that evaluated the changes of VO_2max after exercise training as a secondary outcome in individuals with high blood pressure described a significant increase in VO_2max for endurance and resistance trainings [31].

2.4.4.4. Arterial Stiffness

Two meta-analyses have compared the effect of exercise modalities on PWV. Ashor et al. [32] described PWV improvements with endurance training but not with resistance training or a combination of both endurance and resistance in healthy and CVD individuals. Meanwhile, Zheng et al. [30] found that PWV was improved in CVD individuals by a combination of endurance and resistance training and by endurance training alone.

2.4.4.5. Lipid Profile

The effects of endurance exercise on lipid metabolism in individuals with high blood pressure were evaluated by Fagard in a meta-analysis [31]. Although TG, LDL-C, and HDL-C levels improved, only the latter showed a statistical difference after exercise training.

2.4.4.6. Body Composition

Exercise alone has a low impact on weight loss but it has been observed that it can reduce body fat and increase muscle mass. A meta-analysis [31] evaluating the effects of exercise training on body composition in healthy sedentary normotensive and hypertensive adults reported that endurance training induced a significant net reduction in weight by 1.2 kg, percentage body fat (%BF) by 1.4%, and waist circumference by 2.8 cm. Meanwhile, resistance training induced a significant net reduction in %BF by 0.94%. Lamina et al. [219] showed that eight weeks of interval cycling significantly reduced %BF by 9.91% and waist-to-hip ratio by 0.08 in individuals with high blood pressure lacking comorbidities. Lima et al. [220] compared the effects of endurance training, resistance training, and a combination of endurance and

resistance training on body composition and anthropometric measures in older hypertensive individuals. They reported a significant reduction in fat mass after only 10 weeks of resistance training and a reduction in abdominal and waist circumferences after 10 weeks of endurance training and 10 weeks of resistance training. In contrast, Son et al. [221] showed that 12 weeks of combined resistance and endurance training significantly reduced %BF by 1.35% in 40 obese high blood pressure female adolescents.

2.4.4.7. Cardiac Adaptations

The heart is one of the main end-organ targets affected by high blood pressure. Sustained hypertension triggers several structural and functional adaptations in the heart to maintain homeostasis where left ventricle hypertrophy (LVH) is the most remarkable due to its association with cardiovascular mortality [222,223]. LVH also affects the ability of the ventricle to relax during diastole, process known as diastolic dysfunction, where an increase in left atrium pressure have been described. This raise in atrial pressure is followed by pulmonary congestion and in some cases atrial fibrillation [224]. Reversion of LVH is associated with lower mortality rates due to CVD [225]. Long-term endurance exercise training can also induce cardiac remodeling and LVH, but this remodeling process involves different molecular pathways than high blood pressure induced-LVH [226,227]. Interestingly, exercise training has shown a LVH reversion in individuals with high blood pressure [226,228]. In a randomized controlled study, Kokkinos et al. [159] examined the effects of 16 weeks of cycling at moderate intensity three times per week on LVH in 46 high blood pressure adults (mean age 57.5 years old). They found significant reductions in interventricular septal thickness, left ventricle mass, and left ventricle mass index. A prospective study by Turner et al. [229] evaluated the effects of seven weeks of 30 to 50

minutes of endurance training (brisk walking, jogging, or cycling) four times per week at 60-80% HR_{max} on LVH in 18 high blood pressure older adults (mean age 66.5 years old) that were divided into an exercise group (n = 11) or sedentary group (n = 7). They described a significant decrease in left ventricle wall thickness and left ventricle mass index in the exercise group with no observed changes in the control group. A randomized controlled trial by Hinderliter et al. [230] demonstrated that six months of 55 minutes of endurance training (cycling, walking, or jogging), where 20 minutes were designated for warming up and cooling down and 35 minutes for exercise at 75-85% HR_{max}, three to four times per week, significantly reduced left ventricle relative wall thickness and posterior wall thickness in 82 overweight subjects with high blood pressure. Rinder et al. [231] compared the effects of six months of endurance exercise training (brisk, walking, jogging, running, or cycling) three times per week at a progressive intensity (60 to 85% HRR) versus pharmacological treatment (hydrochlorothiazide) on LVH in 28 older adults (mean age 65.9 years old) with high blood pressure. Their results suggested that exercise training was as effective as drug treatment on LVH regression. Boman et al. [232] evaluated the left ventricular structure and function between 212 sedentary hypertensive subjects, 236 hypertensive subjects that exercised 30 minutes or less twice per week, and 510 hypertensive subjects who exercised more than 30 minutes twice per week. They found a significantly lower left ventricle mass, left ventricle mass indexed to height, and left ventricle wall thickness in both exercise groups in comparison to the sedentary group. No differences were found in cardiac function among the three groups. In a follow-up study, Palatini et al. [33] classified 454 hypertensive subjects into sedentary, mild-exercisers, and exercisers cohorts according to a standardized questionnaire assessing physical activity and compared the evolution of the cardiac structure by echocardiography amongst groups. They observed that the exercise group had a reduced risk to

develop LVH compared to the sedentary group. Pitsavos et al. [191] used a randomized controlled study to examine the effects of 16 weeks of cycling during ~45 minutes at 60-80 HR_{max} three times per week on LVH development in 40 adults with high blood pressure (mean age 53.5 years old). They observed a significant reduction in the left ventricle mass index over the duration of the study. Zheng et al. [233] in a randomized controlled trial, compared the effects of six months of cycling during 30 minutes at the first ventilatory threshold three times per week on ventricular function in 50 hypertensive patients. They described an improvement in left ventricular diastolic function measured by left atrial volume index, peak mitral filling velocities during early (E) and late (A) diastole E/A ratio, deceleration time of the mitral E wave, and tissue Doppler Ea/Aa ratio in the exercise group. Andersen et al. [234] found in a randomized controlled study that 6 months of 60-minute soccer training twice per week in 31 hypertensive adults (mean age 46 years old) significantly improved diastolic function and did not enhance LVH. Conversely, two prospective studies [235,236] did not observe changes in LV dimensions, LV mass, or diastolic function after 6 months of endurance exercise training in 15 individuals with high blood pressure or after ~16 months of endurance exercise training in 32 individuals with high blood pressure, respectively. To date, there is no clinical evidence regarding the effects of resistance training on the heart of individuals with high blood pressure [226]. Additionally, multiple studies have indicated that exercise training benefits the heart by reducing peripheral resistance, reducing resting heart rate, improving contractility, increasing the diameter of the coronary arteries, and favoring collateral coronary circulation growth [226,228,237,238].

2.4.4.8. Vascular Adaptations

Exercise-induced vascular functional and structural adaptations have been extensively reported in healthy and CVD individuals [21,239]. These adaptations are vessel specific (e.g. elastic, conduit, and resistance arteries) [21] and go beyond those vessels that supply blood to contracting muscles (e.g. carotid artery) [240,241].

Favorable functional adaptations have been described through improvements in flow-mediated dilation (FMD) in individuals with high blood pressure [167,242]. As an illustration, Nualnim et al. [243] performed a 12-week intervention where they compared FMD before and after swimming training (45 minutes, 70-75% HR_{max}, 3-4 times per week) or relaxation exercises in 43 individuals with high blood pressure. They observed a 2.2-fold significant increase in FMD in the swimming group. Westhoff et al. [244] also showed a significant improvement in FMD wtihin individuals with high blood pressure that completed a 12-week treadmill program at blood lactate leves of 2.5 (0.5) mmol/L during 30 to 36 minutes. To compare the effects of exercise modalities on FMD, Beck et al. [215] randomly allocated 43 individuals with high blood pressure to either a resistance training, walking/running training, or control group. Both exercise modalities showed a significant improvement in FMD in comparison to the control group, but no appreciable differences were observed between the two exercise modalities. Additionally, to evaluate the effects of exercise duration on FMD, Swift et al. [245] compared the evolution in FMD after 6-month of endurance training at 50% HR_{max} three times per week in 155 obese postmenopausal women with high blood pressure. Subjects were randomly assigned to complete 4, 8, or 12 kilocalories per kilogram of energy expenditure per week or to a no exercise control group. All three exercise groups showed significant improvements in FMD compared to the control group, but no significant statistical differences were found among the exercise groups.

Further, to compare the effects of exercise intensity on FMD, Molmen-Hansen et al. [192] randomly assigned 88 high blood pressure patients to 12 weeks of HIIT, moderate-intensity endurance training, or to a control group. They reported a significantly increase in FMD within the HIIT group only. In contrast, Westhoff et al. [185] did not find any changes in FMD in individuals with high blood pressure after 12-weeks of 24-30 minutes of upper body exercise (arm-cranking) at blood lactate levels of 2.0 (0.5) mmol/L, three times per week.

The classic approach to evaluate vascular structural adaptations is to analyze arterial diameter, wall thickness, or peak blood flow measured by plethysmography [21]. The latter reflects the ceiling structural capacity of the vessels. As examples, Higashi et al. [167] and Beck et al. [246] demonstrated improvements in forearm blood flow in individuals with high blood pressure after 12-weeks of endurance training and 8 weeks of resistance training, respectively, which indicates an structural improvement in resistance vessels.

2.4.4.9. Inflammation

Exercise training has the potential to reduce levels of CRP and IL-6 in both healthy and diseased individuals [247,248]. However, limited evidence exists regarding the effects of exercise on inflammation in individuals with high blood pressure. Lamina et al. [249] in a randomized controlled trial, reported that eight weeks of interval cycling at 60-79% HR_{max} for 45-60 minutes significantly reduced CRP in 140 individuals with high blood pressure compared to a sedentary control group composed of 105 individuals with high blood pressure.

2.4.4.10. Oxidative Stress

The effects of exercise on oxidative stress have been studied more extensively in animal hypertensive models than in humans [250,251]. Only a few clinical studies have explored the relationship between chronic exercise in individuals with high blood pressure and oxidative stress biomarkers. Feairheller et al. [252] evaluated the changes in urinary 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-PGF2α), urinary nitric oxide metabolites, and plasma total antioxidant capacity (TAC) in 94 sedentary individuals with high blood pressure after 6 months of endurance training three times per week at 70% VO_2max. They found significant increases in both 8-iso-PGF2α and TAC levels with a concurrent significant decrease in nitric oxide metabolites, which might indicate improvements in antioxidant capacity. Beck et al. [246] randomly assigned 43 young adults with high blood pressure into three groups (resistance training, endurance training, and control) and analyzed pre- and post- antioxidant capacity and lipid peroxidation in an eight-week trial. Both exercise groups significantly increased plasma antioxidant capacity and significantly reduced 8-iso-PGF2α plasma levels. Dantas et al. [253] evaluated the effects of 10-week resistance training on oxidative stress in 25 elderly women with high blood pressure in a randomized, controlled trial. They described significantly increased levels of plasma TAC and a significant reduction in plasma malondialdehyde (MDA).

2.4.5. The Endothelium and Atherosclerosis

The endothelium is an active metabolic barrier between that can locally modulate the vascular tone and the immune, thrombotic, and inflammatory responses [254]. Each endothelial cell is surrounded by a plasma membrane with specific receptors (e.g., glycocalyx, ion channels,

receptor-tyrosine kinases) to sense changes in shear stress. Those receptors in turn transmit a signal to the nucleus through mechanotransduction of the cytoskeleton [255].

The endothelium can be considered as one of the most important endocrine glands in the body. In direct contact with the blood, endothelial cells can release several soluble factors that can regulate blood flow, hemostasis, vascular tone, inflammation, angiogenesis, the immune system, and other specific functions. From a practical standpoint, these soluble factors can be divided according to their function [256-258]:

Vascular Tone

- The endothelial nitric oxide synthase (eNOS) catalyzes the production of NO from L-arginine. The enzyme is activated via changes in intracellular calcium in response to shear stress patterns or via a receptor-mediated process (e.g. acetylcholine, bradikinine). Released NO activates guanylate cyclase in smooth muscle cells, converting GTP to cGMP. This activates a protein kinase that inhibits the influx of Ca^{2+} into the smooth muscle, which in turn decrease the binding between calcium and calmodulin producing a decrease in the phosphorylation of myosin and further in smooth muscle tension (vasodilatation).
- Leukotrienes are synthesized from arachidonic acid. They produce vasoconstriction and have effects on increasing permeability, adherence, and chemotaxis. Endothelial cells do not contain 5-lipoxygenase, so they interact with neutrophils to metabolize leukotrienes.
- Prostacyclin is also synthesized from arachidonic acid by endothelial cells in response to inflammatory mediators, like interleukin-1 (IL-1) that acts as a vasodilator and inhibits platelet aggregation and thrombosis.

- Endotehlin-1 (ET-1). ET-1 binds to vascular smooth muscle receptors and produce vasoconstriction. In addition, ET-1 stimulates smooth muscle cell proliferation.

Immune System and Inflammation

- Chemokines (α and β chemokines and fractalkine) are produced in processes like inflammation and cancer. They have anti-inflammatory properties by releasing decoy receptors for TNF-α and IL-1.
- Adhesion molecules. Endothelial cells mediate the adhesion of leucocytes expressing in their surface E-selection, P-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule (VCAM). Their expression can be upregulated by inflammatory cytokines. Platelet activating factor (PAF) also upregulate adhesion factors for leucocytes and platelets. The mechanisms involve interaction of the platelet glycoprotein IIb/IIIa with fibrinogen and endothelial vitronectin receptors.

Hemostasis and Coagulation

- von Willebrand factor (vWF). vWF is a protein stored in the Weibel–Palade bodies of endothelial cells. They have a role in platelet recruitment and thrombus formation. vWF is released into the blood stream where it stabilizes factor VIII and is associated with collagen VI in the sub-endothelium.
- Lipid mediator platelet-activating factor (PAF). PAF promotes the activation of platelets and their adhesion to the endothelial cells.
- Thromboxane A2 (TXA2). TXA2 has prothrombotic properties and is a potent vasoconstrictor.
- Tissue Factor (TF). TF initiates coagulation by binding to factor VIIa.

Angiogenesis

- Vascular endothelial growth factor (VEGF). These factors can induce the formation of new vessels from the endothelium. Also, they contribute to the inflammatory response and vascular tone by releasing adhesion molecules and NO, respectively.

Fibrinolysis

- Tissue-type plasminogen activator (t-PA). t-PA catalyzes the conversion of plasminogen to plasmin, which is responsible for clot breakdown.

Atherosclerosis is a vascular condition characterized by a defective endothelium, chronic inflammation, oxidative stress exacerbation and the formation of a waxy substance inside the inner layer of large and medium-sized arteries known as plaque [259,260]. A plaque is filled with lipids, calcium, debris, inflammatory cytokines, and ROS [261]. Atherosclerosis is the first cause of death worldwide and can lead to catastrophic cardiovascular diseases like coronary artery disease, stroke, heart failure, and peripheral artery disease [1].

According to the most current theory, the physiopathology of atherosclerosis involves 3 stages: fatty streak formation, plaque progression, and plaque disruption [262]. The buildup of a plaque starts in the first decades of life with the accumulation of fatty streaks inside the inner portion of an artery. Four cellular mechanisms have been identified: endothelial dysfunction, lipoprotein entry and modification, leukocyte recruitment, and foam cell formation [260,263]. Endothelial dysfunction is considered the first step in plaque development. An initial trauma to the endothelium is necessary to trigger a disturbance in its metabolic balance to maintain homeostasis. This trauma can be originated due to a decrease mechanical stimulus provided by ESS, an increase in cyclic stretch due to high blood pressure, and/or by a chemical toxic environment. A reduction

in endothelial shear stress is associated with plaque development (e.g. branches of arteries) and that blood flow patterns can also modulate this process (e.g. oscillatory blood flow upregulates pro-atherogenic genes and downregulate anti-atherogenic genes) [69]. An increase on sustained cyclic stretch have been reported to be involved in every stage of plaque development (e.g. infiltration of LDL inside the wall, expression of adhesion molecules and scavenger receptors, and metalloproteinases production). Regarding chemical stimulus, increased levels of glycemia, lipids (TG, LDL-C, VLDL-C), or tobacco-related substances can interact with endothelial cells and can boost the ROS production and trigger several inflammatory pathways. Once the endothelium cannot act as an effective barrier for the circulatory factors, LDL-C enters the intima, binds to proteoglycans and starts accumulating in the sub-endothelial space. Several modifications to LDL-C structure (e.g. oxidation, glycation) promotes an inflammatory cycle, expression of leukocytes adhesion molecules, and foam cell formation. Then, the expression of adhesion molecules (e.g. VCAM-1, ICAM-1, E-selectin, P-selectin) in the apical part of endothelial cells attract monocytes and T lymphocytes to the site of injury. In addition, chemoattractant signals (e.g. MCP-1) induce direct diapedesis of these leukocytes into the sub-endothelial space. Simultaneously, inflammatory cytokines (e.g. TNF-α, IL-1), ROS, tissue factor, matrix metalloproteinases, and platelet derived growth factor (PDGF) are released by monocytes while T lymphocytes deregulate the adaptive immune response. Next, monocytes are differentiated into macrophages with scavenger receptors that detect and internalize modified LDL-C. This process is not controlled by inhibitory feedback, so large amounts of modify LDL will start to accumulate inside the macrophages giving them a foam-like appearance. Foam cells then release more inflammatory cytokines while some of them enter in apoptosis and generate debris. Further accumulation of foam cells, debris, and lipids forms the center of the plaque as it continues to progress due to the migration of smooth muscle cells

from the media to the intima layer promoted by inflammatory cytokines and PDGF. Smooth muscle cells also start producing more collagen matrix that surrounds the core resulting in a mature fibrous plaque. Finally, smooth muscle cells release matrix metalloproteinases which degrade small portions of the fibrous cap, leading to micro ruptures, thrombi activation, and plaque disruption [264].

2.4.6. Exercise-Induced Blood Flow Patterns

More than 50% of the cardiovascular benefits of exercise are explained by an underlying mechanism different than the reduction of risk factors [20]. During exercise, cardiac output increases that, in turn, produces a rise in ESS [21]. Depending on the intensity of the exercise, a transition from laminar to turbulent flow can be observed [68]. This hemodynamic stimulus has shown to induce anti-atherogenic adaptations on the vasculature that contribute to the reduction of CVD [21,23,265]. *In vitro* cellular and *in vivo* animal studies have been commonly employed to describe changes on gene expression of endothelial cells exposed to shear stress and more than 3,000 endothelial genes have been identified to be affected by an increase in ESS [266]. Classically, studies have reported an upregulation of eNOS, phosphorylation of eNOS serine-1177 by Akt, an upregulation of SOD, and a down regulation of adhesive proteins (e.g. VCAM-1, ICAM-1) following an exposure of a minimum of 6 hours of high-ESS [23,34,66,266-273]. Regarding blood flow patterns, the most common finding has been that oscillatory blood flow induces an upregulation of atherogenic genes and a downregulation of anti-atherogenic genes on endothelial cells in comparison to anterograde laminar flow [23].

2.4.7. Summary

In summary, the endothelium has a key role in the development and maintenance of high blood pressure and atherosclerosis. Exercise training can favor the balance of endothelial function towards a healthier endothelium phenotype in individuals with high blood pressure, which in turn improve cardiovascular risk factors and health outcomes. For individuals with elevated blood pressure or stage 1 hypertension, exercise training is a recommendation class IA [7]. However, only 21.6% of the US adult population fulfill the minimal requirements of daily physical activity [1] and a large dropout rate has been described in cardiac rehabilitation programs [35]. The incorporation of nontraditional modalities of exercise that are supported by scientific evidence is an attractive idea to overcome these issues. Therefore, boxing training as a nontraditional form of exercise that combines endurance, coordination, and strength in an enjoyable environment could improve the health of individuals with elevated blood pressure or stage 1 hypertension by reversing several pathological pathways involved with high blood pressure, such as endothelial dysfunction, inflammation, oxidative stress, arterial stiffness, and low-ESS.

CHAPTER 3: METHODS

3.1. Experiment 1: Randomized Controlled Trial

3.1.1. Participants

Participants were recruited from the University of Texas at El Paso and its surroundings. They were identified by a preliminary blood pressure screening and a health questionnaire. The cohort consisted of subjects who met the following inclusion criteria: (1) ≥18 years old, (2) SBP between 120-139 mmHg and/or DBP between 80-89 mmHg obtained from 2 different days, (3) an estimated 10-year risk of CVD ≤10%, calculated by the ACC/AHA Pooled Cohort Equations, and (4) no current participation in 3 or more days per week of endurance or resistance exercise training. Exclusion criteria included non-controlled cardiac, pulmonary, or metabolic diseases, smoking, consumption of nutritional supplements containing antioxidants, and any physical impairment to exercise.

3.1.2. Protocol

The study was a double-blind (both evaluator and participant) randomized, controlled trial. Figure 1 describes the protocol for Experiment 1. An initial brachial blood pressure screening was performed to identify potential participants for the present study. Those with SBP readings between 120-139 mmHg or DBP between 80-89 mmHg were instructed to report to the Clinical Applied Physiology Lab at The University of Texas at El Paso having fasted for a second blood pressure assessment, to confirm the diagnosis of elevated blood pressure or stage 1 hypertension. Then, participants were asked to complete a health questionnaire to rule out any cardiac, pulmonary, or metabolic condition. Once they were cleared to participate, participants started the informed consent process (UTEP IRB Study Number 1364179-3). After obtaining the

consent, their height and weight were measured using a stadiometer (Seca 225, Seca Medical Measuring Systems and Scales, Hamburg, Germany) and a digital scale (Tanita WB-110A, Tanita Corporation, Tokyo, Japan), respectively. Thereafter, participants were asked to lay down in supine position over an examination table for 10 minutes where PWA (Sphygmocor, Xcel, West Ryde, Australia), PWV (Sphygmocor, Xcel, West Ryde, Australia), carotid ultrasound imaging, brachial and popliteal FMD, and strain gauge venous occlusion plethysmography (AI6 Arterial Inflow System, D.E. Hokanson Inc., Bellevue, Washington) were performed from the right side of their body. At the end of the first lab visit, they completed the SF-36 questionnaire and were asked to comply with a low nitrate diet for 48 hours. In a second visit, a catheter was placed in the antecubital vein of the participants to collect blood samples, followed by a body composition analysis through dual-energy X-ray absorptiometry (DXA) (Lunar Prodigy, GE Healthcare, Madison, WI), an echocardiographic assessment to determine cardiac dimensions and function (MyLab 25Gold, Esaote, Firenze, Italy), and a cardiopulmonary test using a crank-arm ergometer (Angio V2, Lode, Groningen, Netherlands) to determine their VO_2max (Parvomedics Inc., Sandy, UT) and their ventilatory and lactate thresholds (Lactate Plus, Nova Inc., Boston, MA). Participants were then randomly assigned by a member of the research team who was not involved in the assessments or the analysis into a boxing or a control group using an online number generator (https://www.graphpad.com/quickcalcs/randomize1/). Participants were unaware of the allocation possibilities. A 6-week intervention was designed for each group. Each intervention was supervised by members of the research team who were not involved in the assessments or the analysis. Finally, all the measurements taken in the first two visits were repeated in the same order at the end of the intervention. The evaluator who performed the pre- and post- assessments was blinded to the allocation of each participant.

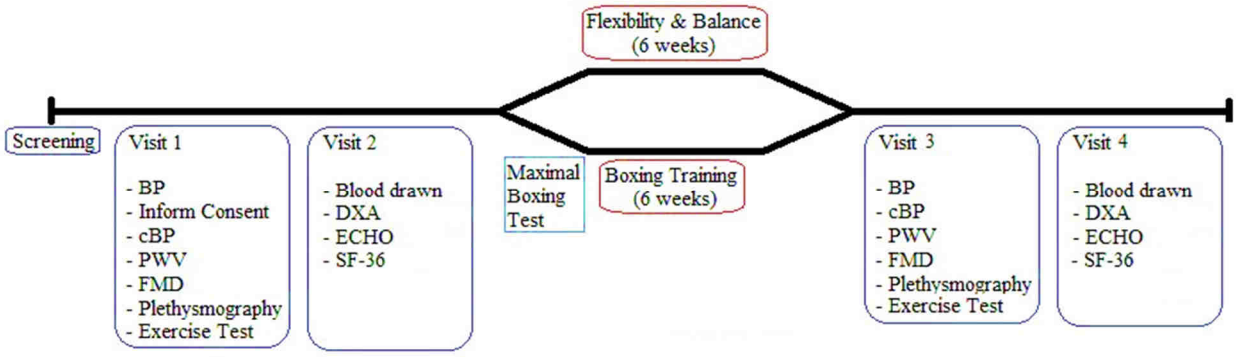

Figure 1. Experiment 1 protocol design.

3.1.3. Interventions

3.1.3.1. Boxing Training

First, in a familiarization visit, participants learned how to wrap their hands and perform basic boxing techniques such as stance and punches while wearing 14-oz gloves. This visit finished with an incremental boxing test that consisted of punching a 100 lb heavy bag (Ringside soft filled leather, Ringside-CSI Fitness 1st, Lenexa, KS) at a fixed force (~20 kg) and with an increase in the punching cadence every 3 minutes. The force was tracked by a sensor attached to the bottom of the heavy bag (UFC Force Tracker) which via a phone app (XFORCE tracker, SEROSE) gave visual feedback of power and rhythm to the participant. The test started at a cadence of 140 punches per minute (ppm) controlled by a metronome (Pro Metronome by EUMLab, Xanin Tech. GmbH.) and was increased 30 ppm every 3 minutes, until fatigue. Fatigue was determined when participants were not able to maintain the punching tempo and they were asked for a 1-minute all-out to finish the test. As depicted in Figure 2, oxygen uptake (VO_2), heart rate (HR), blood lactate, and rate of perceived exertion (RPE) were measured at the end of each 3-minute workload.

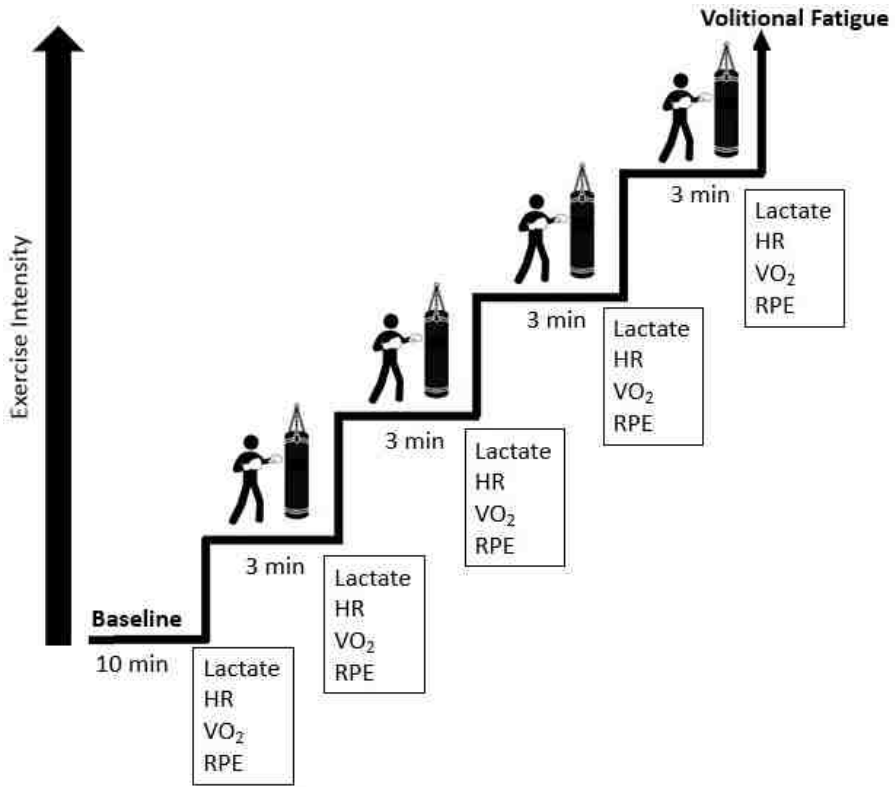

Figure 2. Incremental boxing test design.
HR: heart rate, VO_2: oxygen uptake, RPE: rate of perceived exertion

The boxing training intervention consisted of three exercise sessions per week on nonconsecutive days for six weeks. The workout begun with a 3-minute warm up period where participants actively move their shoulders, elbows, wrists, and finger joints. Participants were then instructed to complete 10 rounds of three minutes with one-minute resting period interspersed as displayed in Figure 3. During the rounds, participants punched a heavy bag (e.g. straight, jab, hook) or did mitt work. The intensity of seven of those rounds was set below their ventilatory and lactate thresholds at approximately 60% HRR or less than 4 on the modified RPE scale (1-10). The intensity of the remaining 3 rounds was set at 90-95% VO_2max and at approximately 95% HRR. Heart rate and RPE were constantly monitored to ensure that each

participant was exercising at the desired intensity. Weekly training characteristics are presented in Appendix A.

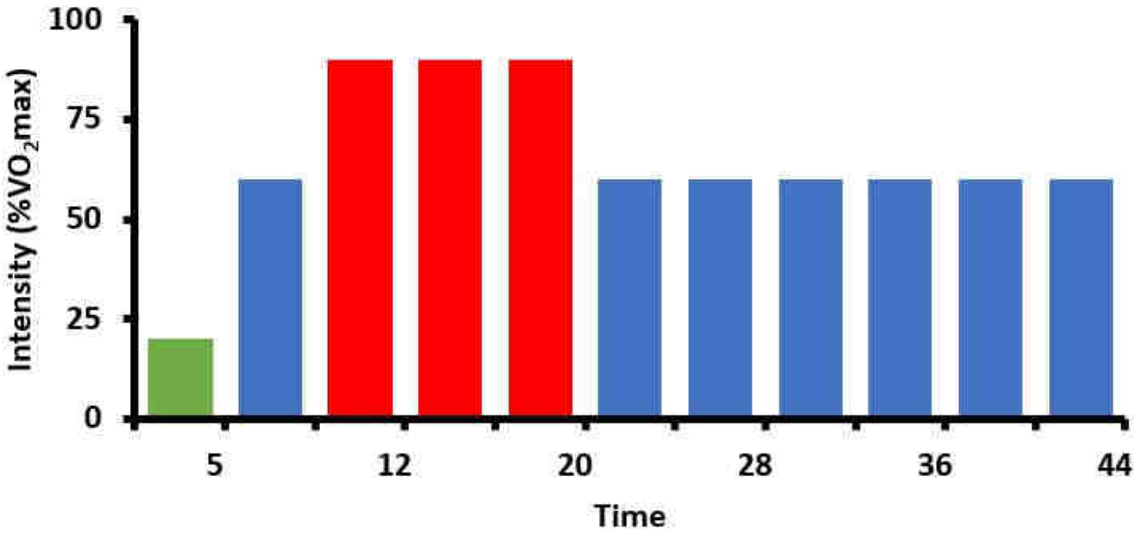

Figure 3. Boxing workout design.

3.1.3.2. Flexibility and Balance Training (Control)

The control group performed 10 minutes of dynamic articular movement, five minutes of unipedal stance, and five minutes of stretching of the upper limbs three days per week for six weeks.

3.1.4. Measurements

3.1.4.1. Brachial Blood Pressure and Heart Rate

Blood pressure assessments were performed according to the ACC/AHA recommendations [7]. Briefly, participants seated in a chair for five minutes with their feet on the floor and their back supported, followed by the recording of blood pressure and resting heart rate

in triplicate with a validated automated brachial blood pressure cuff (BP760, Omnron Healthcare, Inc., Lake Forest, IL).

3.1.4.2. Central Blood Pressure

A cuff-based device for PWA (Sphygmocor Xcel, AtCor Medical, West Ryde, Australia) was attached to the right arm of every participant in supine position after 10 minutes of resting. Each PWA assessment lasted between 60 and 120 seconds: 50-110 seconds to record brachial blood pressure and 10 seconds of sub-diastolic recordings. Central blood pressure waveforms were generated by a validated transfer function [274]. According to manufacturer's recommendations, the blood pressure waveforms were considered acceptable if the overall quality control indices were equal to or above 75%.

The following PWA variables were assessed: cSBP, cDBP, cPP, AIx, and AIx@75. cSBP and cDBP are the estimated blood pressures at the ascendant aortic wall during systole and diastole, respectively. cPP is the difference between cSBP and cDBP. AIx is the ratio between the increase in aortic blood pressure produced by reflected waves in relation to cPP and AIX@75 is the normalization of AIx to 75 bpm [275]. All these variables have been associated with cardiovascular risk [276]. Additionally, Wasted Left Ventricle Energy (LVE_W), a surrogate for left ventricle work and myocardial oxygen demand, was estimated from the pulse pressure curve and the duration of the reflected wave. LVE_W was calculated using the following formula: $LVE_W = ((ED - \Delta t_p) \times (cSBP - Pi)\ \pi/4) \times 1.33322$, where ED is ejection duration, Δt_p is time to arrival of the reflected pressure wave, and Pi is the pressure at the first inflection point marking the onset of reflected aortic pressure wave [277,278].

3.1.4.3. Pulse Wave Velocity

Carotid-femoral pulse wave velocity (PWVcf) is considered the gold standard to determine arterial stiffness [279]. For this procedure, participants were supine over an examination table for 15 minutes and a cuff was placed in the right thigh. During this period, carotid and femoral pulses were palpated. Then the following distances were measured using a metallic tape: carotid to sternal notch, sternal notch to cuff, and femoral to cuff. Once the participant reaches hemodynamic stability, a high-fidelity tonometer was placed over the carotid artery. Pulse waves of the carotid and femoral arteries were simultaneously recorded by the tonometer and the cuff, respectively. PWVcf was determined by dividing the distance obtained through the subtractive method by the delay time between waves [96,280-282].

3.1.4.4. Cardiopulmonary Exercise Testing

An 8-to-12 minutes exercise test on a crank-arm ergometer was performed using the AHA guidelines [119]. The test started at 50 watts (W) and 40 W for male and female participants, respectively, with a 15 W increase for the former and 12 W for the latter, until fatigue. A cadence of 60 rpm was maintained throughout the test. Oxygen uptake and heart rate were continuously monitored. RPE and lactate were determined at the end of each workload. To assess oxygen uptake, participants breathed through a mouthpiece connected via a long tube to the metabolic cart and a nose-clip was placed on the participant's nose to prevent air leakage. Immediately before starting their exercise tests, the participant' earlobe was poked with a micro-lancet to monitor lactate blood levels. VO_2max was defined as the greatest value recorded during the test when the participants accomplish at least three of the following criteria: (1) plateau in oxygen uptake (e.g. <150 ml/min difference between workloads), (2) respiratory exchange ratio

> 1.1, (3) ≥90% predicted maximal heart rate, and (4) blood lactate levels >6 mmol/L [283]. The VO_2max is expressed relative to body mass (ml/kg/min). The first ventilatory threshold and the lactate threshold were determined by the V-slope [284] and the D-max methods [285], respectively.

3.1.4.5. Echocardiography

A two-dimensional echocardiography study was performed according to the recommendations of the American Society of Echocardiography [286,287]. Images were obtained along the parasternal long and short axis, including the apical, subcostal, and suprasternal views). From the parasternal long-axis view, end-diastolic measurements of the septal wall thickness (IVSd)), left ventricle diameter (LVEDD), posterior wall thickness (PWd), and left ventricular end-systolic diameter (LVESD) were obtained to estimate left ventricle ejection fraction (LV EF%) and mass. The LV EF% was calculated as the ratio between LVESD and LVESD. LV mass was estimated by Devereux formula: LV mass = 0.8 (1.04 [(LVEDD + PWd + IVSd)^3- (LVEDD)^3])+ 0.6 g [288]. End-diastolic volume (EDV) and end-systolic volume (ESV) of LV and Stroke Volume were calculated by the Simpson method from the apical 4-chamber and 2-chamber views. Pulsed, continuous and color Doppler were used to evaluate valvular function. Additionaly, lateral tisular Doppler velocity was assessed to evaluate LV diastolic function. Finally, aortic measurements were made from a 2D parasternal long axis-view using the inner edge-to-inner edge (I-I) convention at the Sinus of Valsalva [287,289].

3.1.4.6. Body Composition Analysis

Total body and regional body composition were estimated through DXA. Before the assessment, the equipment was calibrated according manufacturer's instructions. The system calculated the mass of lean soft tissue, fat, and bone mineral for the whole body, trunk, and extremities. DXA is one of the preferred techniques to determine body composition [290].

3.1.4.7. Questionnaire to assess Quality of Life: SF-36

The short-form 36 (SF-36) was created in 1992 to evaluate health-relate quality of life [291]. The SF-36 is a short survey that covers a total of 8 sub-dimensions related to physical and mental health: (1) Physical Functioning, (2) Role Limitations due to Physical Problems, (3) Social Functioning, (4) Bodily Pain, (5) General Mental Health, (6) Role Limitations due to Mental Problems, (7) Vitality, and (8) General Health Perceptions. The SF-36 includes a diverse mixture of continuous item scaling methods and is comprised of 10 items with balanced multi-item response formats (range from 1 to 5), 7 items with a dichotomous response format (1 or 2), and 19 items with non-balanced multi-item response formats (nine items range from 1 to 3 and ten items range from 1 to 6). To obtain the raw score for each sub-dimension, 10 items are reversed. Then, raw values for each sub-dimension are summed. Finally, the raw scores are transformed to a 0-to-100 scale for each sub-dimension [292]. The utility of the SF-36 has been explored in clinical trials in selected groups suffering from physical or mental conditions. Patients with mental illnesses, scored significantly lower in the mental health section in comparison to matched asymptomatic controls. Also, in a 4-week follow-up study, symptoms of chronic cardiovascular conditions were positively correlated with lower scores on the SF-36. In addition, the sub-dimensions of the SF-36 showed correlations above 0.9 with the 140-items Medical Outcome Study. The validity,

reliability, and consistency of this questionnaire have been demonstrated in previous research [293].

3.1.4.8. Endothelial Function Testing

3.1.4.8.1. Flow-Mediated Dilation (FMD)

For brachial FMD, participants were asked to lay down in a supine position over an examination table for at least 10 minutes. A total of six electrodes were attached to their chest in the standard lead II setting, where three electrodes were connected to a high-definition ultrasound machine (MyLab30 Gold Cardiovascular, Esaote, Firenze, Italy) and the other three were connected to an electrocardiogram trigger system (MP150WSW, BIOPAC Systems Inc., Goleta, CA and Frame Grabbing and Digital Data Input modules, Medical Imaging Applications LLC, Coralville IA). The right arm was moved at 80-90° of shoulder abduction over an armrest and a blood pressure cuff was attached to the forearm just below the antecubital fossa. A 12-MHz linear phase array ultrasound transducer (LA435, Esaote, Firenze, Italy) with a transducer holder (Patent pending, UTEP2019-006-PROV) was placed 5 cm above the antecubital fossa to image the right brachial artery according to international guidelines for FMD [77,294,295]. Basal artery diameters and peak systolic blood flow velocities were recorded in basal conditions at every QRS complex captured by the electrocardiogram trigger system using an automated edge-detection software (Vascular Research Tools, Medical Imaging Applications LLC) for 30 seconds. Then, the forearm cuff was inflated to supra systolic pressure (>200 mmHg) for 5 minutes followed by the deflation of the cuff. Brachial artery diameters and blood flow velocities were continuously registered every 3 seconds for 150 seconds, starting at 30 seconds before deflation until 2 minutes after deflation using the automated edge-detection software. Peak

diameters were identified as the single peak diameter observed during the plateau phase after cuff deflation [296]. The reliability of FMD analysis in our lab has already been tested and is described elsewhere [297]. For popliteal FMD, the same procedure is repeated but with the difference that the cuff and the transducer were placed in the leg and in the popliteal fossa, respectively. FMD was calculated as FMD% = 100 x (peak diameter – basal diameter)/basal diameter [298].

3.1.4.8.2. Plethysmography

3.1.4.8.2.1. Forearm and Calf Blood Flow

Forearm blood flow (FBF) and calf blood flow (CBF) were assessed by strain gauge venous occlusion plethysmography (AI6 Arterial Inflow System, D.E. Hokanson Inc., Bellevue, Washington). Participants were in supine position over an examination table where strain gauges were placed at the widest part of the right forearm or calf. Next, an upper-arm cuff for FBF and a thigh cuff for CBF were cycled from 0 to 50 mmHg for seven seconds every 15 seconds to prevent venous outflow. One minute before each measurement, a wrist and an ankle cuff were inflated to 200 mmHg to occlude hand and ankle circulation, respectively. Absolute blood flow was determined by the rate of change of limb circumference (e.g. slope) during the seven-second venous occlusion. FBF and CBF were estimated as the average of three readings in a minute [246].

3.1.4.8.2.2. Forearm and Calf Blood Flow during Reactive Hyperemia

FBF and CBF during reactive hyperemia was measured after five minutes of occlusion of the arm or thigh, respectively. These measurements are a reliable non-invasive alternative to

estimate endothelial function in resistance vessels [299]. Baseline FBF and CBF were recorded for 2 min, then the respective cuff was inflated to 200 mmHg for five minutes and then rapidly deflated. FBF and CBF was measured every 15 seconds for three minutes. Peak FBF and CBF were selected from the highest value of blood flow following deflation of the cuff [246].

3.1.4.9. Carotid Artery Ultrasound

An 8-18 Hz ultrasound transducer (LA435, Esaote, Firenze, Italy) inserted into a neck transducer holder was attached to the right side of the neck of each participant and the mid-section of the common coronary artery was identified in a high-definition ultrasound machine (MyLab30 Gold Cardiovascular, Esaote, Firenze, Italy). Resting arterial diameters and peak systolic blood flow velocities were recorded continuously during 10 seconds at a rate of 10 frames per second using an automated edge-detection software (Vascular Research Tools, Medical Imaging Applications LLC).

Resting ESS was estimated during 10 seconds by Womersley's approximation, using ESS = μ * SR and SR = 2K * V/D, where μ is blood viscosity, SR is shear rate, V is peak systolic velocity, D is artery diameter, K is a complex factor dependent only on the Womersley parameter (α), and $\alpha=(D/2)*(\omega/(\mu/\rho))^{1/2}$, where ω is the angular frequency of the flow pulsation (ω=freq*2π), ρ is blood density, and μ is blood viscosity [300,301]. ESS is expressed in dynes/cm^2.

Blood viscosity and density were calculated using the following formulas [68,302,303]: $\mu_{plasma} = \frac{\exp[-5.64+\frac{1800}{T+273}]}{SR}$, $\mu = \mu_{plasma} * \exp(2.31HCT)$, and $\rho = [1.09HCT + 1.035 * (1 - HCT)]$, where μ_{plasma} is plasma dynamic viscosity expressed in Pa·s, T is temperature expressed in °C, and Hct is Hematocrit expressed as a fraction.

3.1.4.10. Tissue Sampling

3.1.4.10.1. Blood Lactate

Blood lactate was taken via micro-sample from the earlobe and analyzed with an automated lactate analyzer (Lactate Plus, Nova Inc., Boston, MA).

3.1.4.10.2. Hematocrit

Two blood samples were collected from the earlobe using micro-hematocrit capillary tubes (Fisher Scientific, Pittsburgh, PA) and hematocrit readings were performed after centrifugation (HemataStat II Hematocrit Analyzer, Separation Technology Inc., USA).

3.1.4.10.3. Antecubital Vein Blood Collection

After 48 hours of a low nitrate diet under fasting conditions, 20 ml blood samples were obtained from the antecubital vein of each participant. Blood samples were immediately centrifuged to obtain plasma samples, the latter being placed in aliquots at -80 °C until analysis. NOx (Total Nitric Oxide and Nitrate/Nitrite Parameter Assay Kit, R&D Systems), lipid profile (HDL and LDL/VLDL Cholesterol Assay Kit, ab65390, Abcam), CRP (C-Reactive Protein (human) ELISA Kit, 10011236, Cayman), IL-6 (Interleukin-6 (human) ELISA Kit, 501030, Cayman), TNF-α (TNF-α (human) ELISA Kit, 589201, Cayman), F2-isoprostanes (STAT-8-isoprostane ELISA Kit, 500431, Cayman), TAC (Antioxidant Assay Kit, 709001, Cayman), and SOD (Superoxide Dismutase Assay Kit, 706002, Cayman) were performed according the manufacturer's instructions for their respective kit at the core lab of the health sciences building at UTEP.

3.1.5. Statistical Analysis

Data was analyzed using SPSS version 24.0. Normal distribution of the data was examined with the Shapiro-Wilk test and visual inspection. Independent t-tests were conducted to compare demographic variables between groups. A repeated measure general linear model (GLM) with two levels of time (pre and post) and using two groups (Boxing and Control) was employed to compare between- and within-group differences. Fisher's Least Significant Difference (LSD) was selected as the post hoc test and partial eta-squared effect size (η_p^2) as the indicator of effect size. η_p^2 of 0.02, 0.13, and 0.26 were considered small, medium, and large effects, respectively [304]. Significance was established at $\alpha \leq 0.05$. The sample size was determined using the software G*Power 3.1. Based on Izadi et al. [193] results on the effects of six weeks of HIIT on SBP (effect size = 1.73), establishing α at 0.05 and β at 0.2, and assuming a 30% drop out rate, the estimated number of participants per group was 12.

3.2. Experiment 2: Cross Sectional Study

3.2.1. Participants

Participants were recruited from the University of Texas at El Paso and its surroundings. They were identified by a preliminary blood pressure screening and a health questionnaire. The inclusion criteria consisted of: (1) ≥18 years old, (2) SBP between 120-139 mmHg or DBP between 80-89 mmHg obtained from 2 different days, (3) an estimated 10-year risk of CVD ≤10%, calculated by the ACC/AHA Pooled Cohort Equations, and (4) no current participation in 3 or more days per week of endurance or resistance exercise training. Exclusion criteria included

non-controlled cardiac, pulmonary, or metabolic diseases, smoking, consumption of nutritional supplements containing antioxidants, and any physical impairment to exercise.

3.2.2. Protocol

First, height and weight were measured using a stadiometer (Seca 225, Seca Medical Measuring Systems and Scales, Hamburg, Germany) and a digital scale (Tanita WB-110A, Tanita Corporation, Tokyo, Japan), respectively. Next, blood samples were collected from the earlobe using micro-hematocrit capillary tubes (Fisher Scientific, Pittsburgh, PA) followed by centrifugation (HemataStat II Hematocrit Analyzer, Separation Technology Inc., USA) and reading of their respective hematocrit values. Participants were asked to perform two boxing evaluations. The first one was a maximal boxing test that determined VO_2max and the lactate threshold curve as described in Figure 2. The second one, performed at least 48 hours after the first exercise test, consisted of two boxing rounds of three minutes with one-minute of rest in between. During the first and second round, participants punched a 100 lb heavy bag at 60%VO_2max and at 90-95% VO_2max, respectively. Concurrently, diameter and blood flow velocity from the common carotid artery were obtained through Doppler ultrasound at each condition. In addition, measures of heart rate, oxygen uptake, blood lactate, and RPE were obtained at the end of the third minute for each round.

3.2.3. Measurements

3.2.3.1. Carotid Artery Ultrasound Assessment

A total of six electrodes were attached to the chest of the participants in the standard lead II setting: three electrodes were connected to a high-definition ultrasound machine (MyLab30

Gold Cardiovascular, Esaote, Firenze, Italy) and the other three were connected to an electrocardiogram trigger system (MP150WSW, BIOPAC Systems Inc., Goleta, CA and Frame Grabbing and Digital Data Input modules, Medical Imaging Applications LLC, Coralville IA). An 8-12 Hz ultrasound transducer (LA435, Esaote, Firenze, Italy) inserted into a neck transducer holder was attached to the neck of the participants and the mid-section of the common carotid artery identified. Artery diameters and peak systolic blood flow velocities were recorded continuously using an automated edge-detection software (Vascular Research Tools, Medical Imaging Applications LLC) at rest and during exercise as depicted in Figure 4.

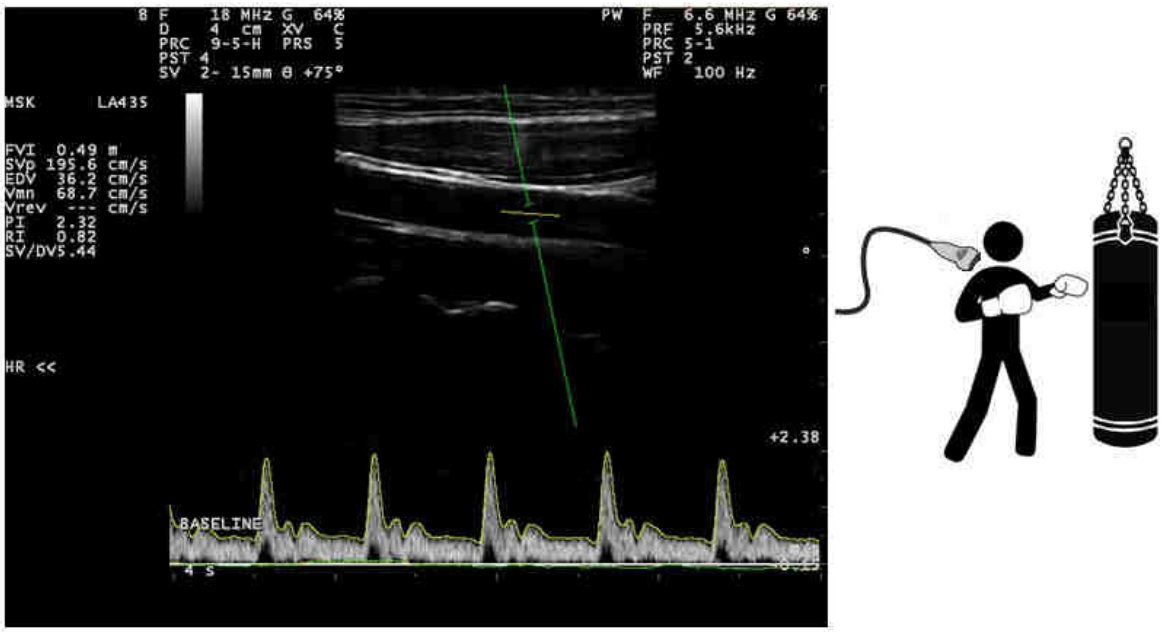

Figure 4. Doppler-ultrasound of the common carotid artery during heavy bag punching.

3.2.3.2. Endothelial Shear Stress Calculations

ESS was estimated during 10 seconds by Womersley's approximation, using ESS = μ * SR and SR = 2K * V/D, where μ is blood viscosity, SR is shear rate, V is peak systolic velocity, D is artery diameter, K is a complex factor dependent only on the Womersley parameter (α)

where $\alpha=(D/2)*(\omega/(\mu/\rho))^{1/2}$, ω is the angular frequency of the flow pulsation (ω=freq*2π), ρ is blood density, and μ is blood viscosity [300,301]. ESS is expressed in dynes/cm^2.

Blood viscosity and density were calculated using the following formulas [68,302,303]: $\mu_{plasma} = \frac{\exp[-5.64+\frac{1800}{T+273}]}{SR}$, $\mu = \mu_{plasma} * \exp(2.31HCT)$, and $\rho = [1.09HCT + 1.035 * (1 - HCT)]$, where μ_{plasma} is plasma dynamic viscosity expressed in Pa·s, T is temperature expressed in °C, and Hct is Hematocrit expressed as a fraction.

3.2.3.3. Blood Flow Patterns

Reynolds number (Re) is a dimensionless ratio of blood inertial forces to viscous forces. For a given vessel geometry, Re determines whether the flow will be laminar or turbulent [305-307]. Re was calculated using Re=(V*D* ρ)/ μ, where V is peak blood flow velocity, D is artery diameter, ρ is blood density, and μ is blood viscosity [307]. To determine the onset of turbulence under pulsatile flow conditions, peak Re critical was calculated using $Re_{peak(cr)}=169*\alpha^{0.83}*St^{-0.27}$, where St is the Strouhal number St=freq*D*V and α is the Womersley parameter [308].

3.2.4. Statistical Analysis

Data was analyzed using SPSS version 24.0. Normal distribution of the data was examined with the Shapiro-Wilk test and visual inspection. The assumption of sphericity was evaluated by Mauchly's test and corrected by the Greenhouse-Geisser method when it was necessary. To compare ESS between resting and the two exercise conditions, a one-way repeated measures ANOVA with Fisher´s LSD as post-hoc analysis was employed. Significance was established at $\alpha \leq 0.05$. Effect size was determined by Cohen's *d*, where 0.2 is a small effect size, 0.5 is a medium effect size, and 0.8 is a large effect size [309]. According to our preliminary data

in cycling, a η_p^2 of 0.948 was obtained for exercise-induced ESS in the carotid artery at three exercise intensities. Using G*Power at a level of significance of 0.05 with a power of 0.8, the minimum number of participants that is required was eight. Assuming a 30% drop out rate, the estimated number of participants required was 10.

CHAPTER 4: RESULTS

4.1. Experiment 1: Randomized Controlled Trial

4.1.1. Participants

Initially, 38 individuals were assessed for eligibility from June to August of 2019. Fourteen subjects were excluded because their blood pressure did not meet the inclusion criteria. As Figure 5 exhibits, a total of 24 participants were randomly allocated to one of the two groups. Only 1 participant was lost for follow up assessments in the control group, leaving 12 participants in the boxing group and 11 participants in the control group that were finally analyzed. All analyzed participants were college students.

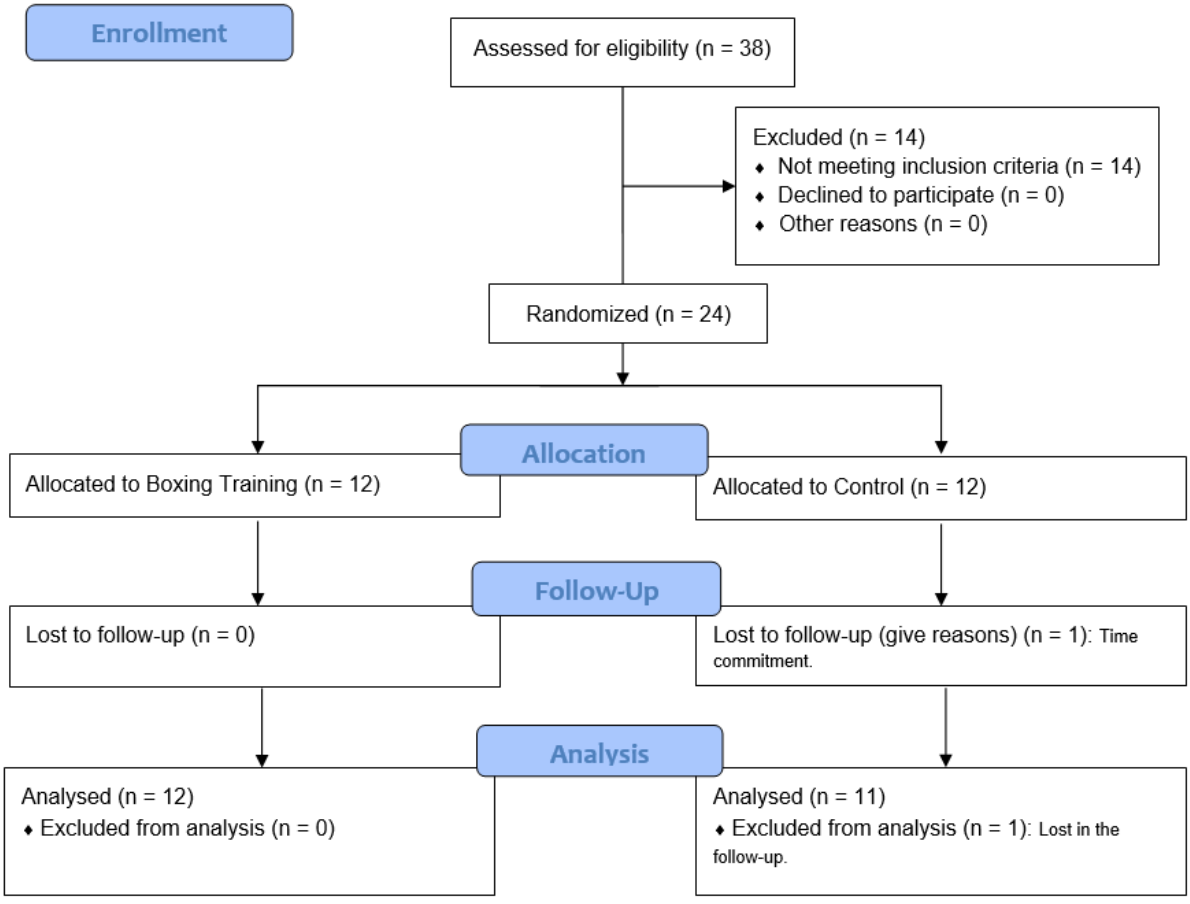

Figure 5. Flow chart of participants.

All variables were normally distributed except for age. All data is presented as mean and standard deviation, unless otherwise stated. The baseline demographic characteristics of both groups are summarized in Table 4. No difference was found between groups regarding age ($U = 86.0$, $p = 0.235$), height ($t(21) = 0.39$, $p = 0.698$), weight ($t(21) = 0.78$, $p = 0.442$), hematocrit ($t(21) = -0.06$, $p = 0.953$), systolic blood pressure ($t(21) = -0.98$, $p = 0.339$), and diastolic blood pressure ($t(21) = -0.301$, $p = 0.766$) before the intervention.

Table 4. Demographic characteristics of the participants.

	Boxing Training			**Control**			
	Male	*Female*	*Total*	*Male*	*Female*	*Total*	*P*
	n = 8	n = 4	N = 12	n = 7	n = 4	N = 11	
Age (y)	27.6 (6.7)	23.5 (0.6)	26.3 (5.7)	26.0 (4.9)	22.0 (0.8)	24.6 (4.3)	0.235
Height (m)	1.7 (0.1)	1.5 (0.1)	1.7 (0.1)	1.7 (0.1)	1.6 (0.1)	1.7 (0.1)	0.698
Weight (kg)	97.7 (24.9)	72.4 (17.9)	89.3 (25.2)	100.6 (17.9)	88.8 (11.7)	96.3 (16.4)	0.442
Hct (%)	49.3 (3.4)	46.0 (3.3)	48.0 (3.7)	49.0 (2.9)	46.0 (4.2)	47.9 (3.5)	0.953
SBP (mmHg)	130.0 (7.2)	113.3 (4.6)	124.4 (10.3)	124.7 (13.3)	110.0 (11.8)	119.4 (14.3)	0.339
DBP (mmHg)	84.9 (6.1)	83.8 (2.5)	84.5 (5.1)	83.9 (4.7)	84.0 (4.1)	83.9 (4.2)	0.766

Data expressed as mean (SD). Hct: Hematocrit; SBP: systolic blood pressure; DBP: diastolic blood pressure.

Compliance to the boxing training protocol was 98.1%. Overall, 95.4% and 100% of the target heart rates were sustained during the three high-intensity rounds and the seven low-intensity rounds, respectively. Additionally, participants reported a mean RPE of 8.3 and 2.8 for the high-intensity and low-intensity rounds, respectively (Figure 6). Meanwhile, the compliance to the flexibility and balance training was 27.3% in the control group.

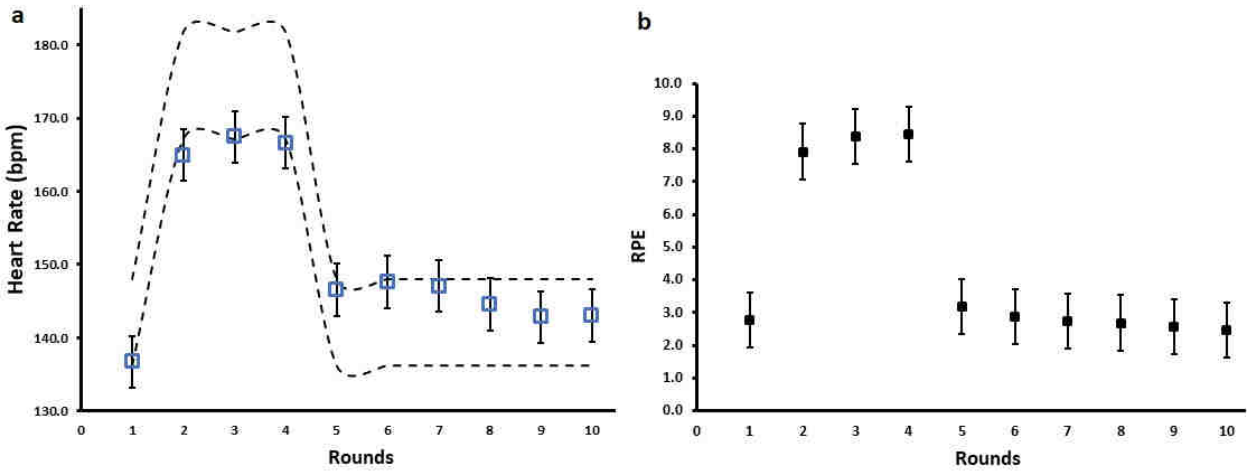

Figure 6. Heart rate and rate of perceived exertion during boxing training expressed as mean (SD). a) Heart rate during boxing training. 95% CI of the target heart rate for each round are represented as dashed lines; b) Rate of perceived exertion at the end of each round. RPE: rate of perceived exertion, bpm: beats per minute.

No adverse cardiovascular effects were reported throughout the intervention. Meanwhile, 3 participants experienced anterior shoulder tenderness when punching during the first week of training that was relieved in the subsequent weeks.

4.1.2. Blood Pressure

Significant group x time interactions were observed for SBP ($F(1,21) = 32.34$, $p < 0.001$) and DBP ($F(1,21) = 39.54$, $p < 0.001$). No differences were observed in SBP ($F(1,21) = 0.96$, $p = 0.339$) and DBP ($F(1,21) = 0.09$, $p = 0.766$) between groups at baseline.

Six weeks of boxing training largely decreased systolic blood pressure ($F(1,21) = 48.89$, $p < 0.001$, $\eta_p^2 = 0.700$) and diastolic blood pressure ($F(1,21) = 78.48$, $p < 0.001$, $\eta_p^2 = 0.789$) in individuals with elevated blood pressure and stage 1 hypertension. Additionally, there was a significant reduction in diastolic blood pressure ($F(1,21) = 19.03$, $p = 0.001$, $\eta_p^2 = 0.475$) after the intervention in the boxing group compared to the control group. No differences were found

before and after the intervention in the control group regarding systolic blood pressure (F(1,21) = 1.39, p = 0.252, η_p^2 = 0.062) and diastolic blood pressure (F(1,21) = 0.05, p = 0.825, η_p^2 = 0.002) (Table 5 and Figure 7).

Table 5. Brachial blood pressure changes following 6 weeks of intervention.

	Boxing Training					Control				
	Before	After	Δ	*P*	η^2p	Before	After	Δ	*p*	η^2p
SBP (mmHg)	124.4 (10.3)	108.4 (7.7)	-16.0	**<0.001**	0.700	119.4 (14.3)	122.2 (13.5)	2.8	0.252	0.062
DBP (mmHg)	84.5 (5.1)	74.2 (5.0)	-10.3	**<0.001**	0.789	83.9 (4.3)	84.2 (6.0)	0.3	0.825	0.002

Data expressed as mean (SD). SBP: systolic blood pressure; DBP: diastolic blood pressure

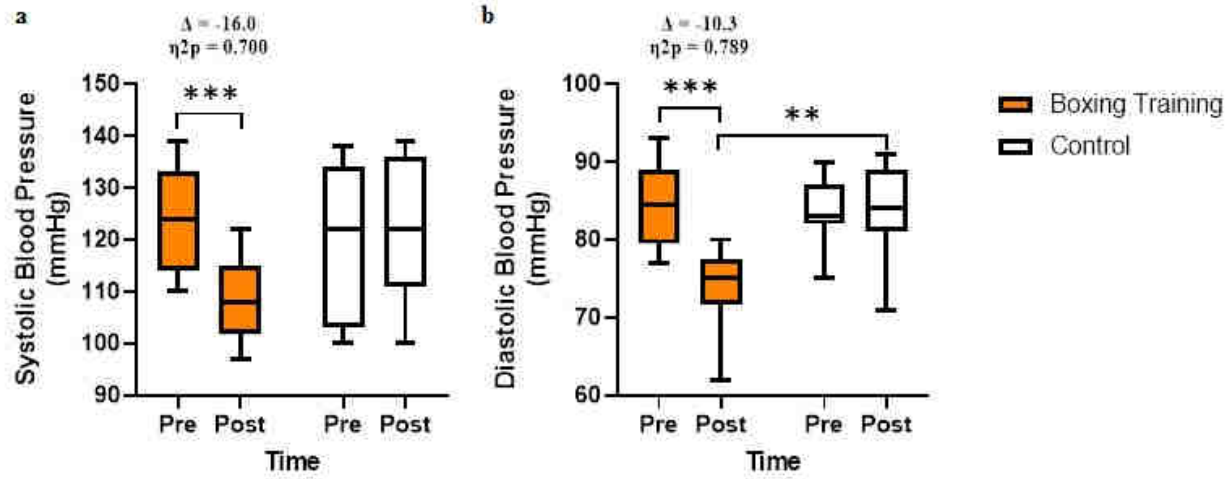

Figure 7. Box plots of brachial blood pressure changes after boxing training. a) Systolic blood pressure; b) Diastolic blood pressure. *** p < 0.001 ** p < 0.01

4.1.3. Pulse Wave Analysis

Significant group x time interactions were only observed for cSBP ($F(1,21) = 4.29$, $p = 0.05$). Meanwhile, there were no significant interactions for cDBP ($F(1,21) = 1.52$, $p = 0.231$), cPP ($F(1,21) = 0.52$, $p = 0.479$), AIx ($F(1,21) = 1.06$, $p = 0.314$), AIx@75 ($F(1,21) = 0.20$, $p = 0.658$), and LVE_w ($F(1,21) = 0.46$, $p = 0.504$). No differences were observed in cSBP ($F(1,21) = 0.02$, $p = 0.896$), cDBP ($F(1,21) = 0.22$, $p = 0.646$), cPP ($F(1,21) = 0.59$, $p = 0.451$), AIx ($F(1,21) = 0.16$, $p = 0.694$), AIx@75 ($F(1,21) = 0.83$, $p = 0.373$), and LVE_w ($F(1,21) = 0.77$, $p = 0.390$) between groups at baseline. A large reduction in cSBP ($F(1,21) = 13.15$, $p = 0.002$, $\eta_p^2 = 0.385$) was observed in the boxing training group following the intervention (Table 6 and Figure 8). Additionally, no significant group x time interaction was detected in the duration of the reflected wave ($F(1,21) = 2.99$, $p = 0.098$).

Table 6. Central blood pressure changes following 6 weeks of intervention.

	Boxing Training			Control			Interaction	Group	Time
	Before	After	Δ	Before	After	Δ	*p*	*p*	*p*
cSBP (mmHg)	114.5 (10.7)	106.5 (6.3)	-8.0	113.9 (11.0)	112.5 (10.0)	-1.4	**0.050**	0.476	0.008
cDBP (mmHg)	80.8 (9.0)	75.7 (8.0)	-5.1	79.0 (9.7)	77.2 (11.2)	-1.8	0.231	0.972	0.020
cPP (mmHg)	33.6 (4.1)	31.0 (3.6)	-2.6	34.8 (3.3)	33.8 (7.1)	-1.0	0.479	0.207	0.129
AIx (%)	15.0 (10.3)	5.6 (17.4)	-9.4	16.8 (12.1)	13.5 (7.0)	-3.3	0.314	0.271	0.040
AIx@75 (%)	12.3 (11.6)	3.3 (17.3)	-9.0	16.9 (12.7)	10.4 (7.4)	-6.5	0.658	0.213	0.011
LVE_w (dynes/s/cm^2)	1217.5 (509.1)	764.9 (606.1)	-452.6	1422.0 (607.5)	1132.6 (415.0)	-289.4	0.504	0.150	0.006

Data expressed as mean (SD). cSBP: central systolic blood pressure; cDBP: central diastolic blood pressure; cPP: pulse pressure; AIx: augmentation index; AIx@75: augmentation index at 75 beats per minute; LVE_W: left ventricle energy wasted.

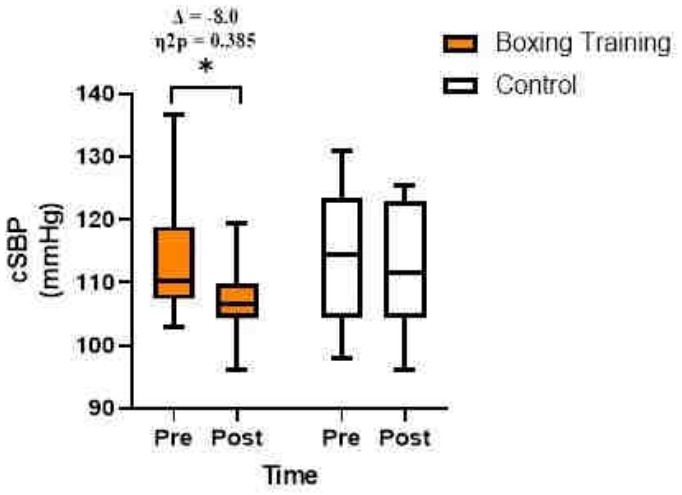

Figure 8. Box plots of central blood pressure changes after boxing training. a) Central systolic blood pressure (cSBP); b) Central diastolic blood pressure (cDBP). * $p < 0.05$

4.1.4. Arterial Stiffness

There was no significant group x time interaction for PWVcf ($F(1,21) = 0.30$, $p = 0.096$). PWVcf was similar between groups at baseline ($F(1,21) = 0.38$, $p = 0.545$) and post training (ANOVA DATA) (Figure 9).

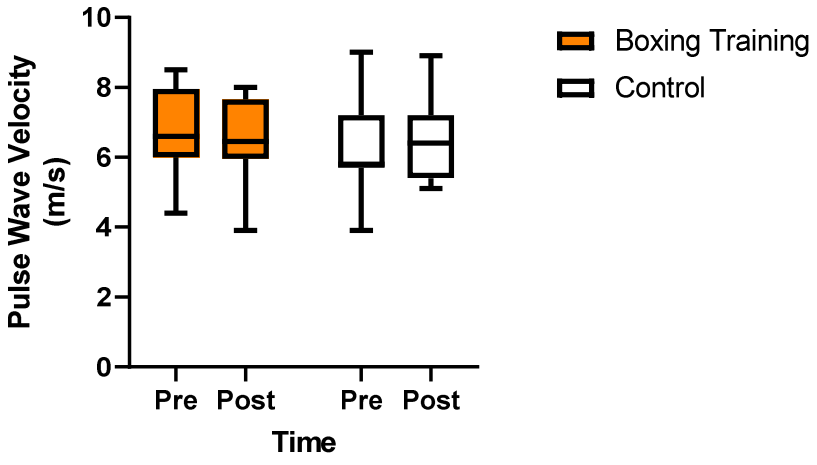

Figure 9. Box plots of Pulse Wave Velocity before and after the intervention.

4.1.5. Cardiorespiratory Fitness

Significant group x time interactions were observed for VO_2max ($F(1,21) = 60.08$, $p < 0.001$), power output ($F(1,21) = 27.67$, $p < 0.001$), lactate threshold ($F(1,21) = 15.59$, $p = 0.001$), and ventilatory threshold ($F(1,21) = 14.91$, $p = 0.001$). No differences were observed in VO_2max ($F(1,21) < 0.01$, $p = 0.964$), power output ($F(1,21) = 0.28$, $p = 0.601$), ventilatory threshold ($F(1,21) = 3.51$, $p = 0.075$), and lactate threshold ($F(1,21) = 2.04$, $p = 0.168$) between groups at baseline. Six weeks of boxing training led to a large increase in VO_2max ($F(1,21) = 70.17$, $p < 0.001$, $\eta_p^2 = 0.770$), power output ($F(1,21) = 31.11$, $p < 0.001$, $\eta_p^2 = 0.597$), ventilatory threshold ($F(1,21) = 26.53$, $p < 0.001$, $\eta_p^2 = 0.558$), and lactate threshold ($F(1,21) = 20.92$, $p < 0.001$, $\eta_p^2 = 0.499$). Meanwhile, a significant large reduction in VO_2max ($F(1,21) = 7.35$, $p = 0.013$, $\eta_p^2 = 0.259$) was observed in the control group at the end of the intervention (Table 7 and Figure 10).

Table 7. Changes on exercise capacity following 6 weeks of intervention.

	Boxing Training					Control				
	Before	After	Δ	*P*	η^2p	Before	After	Δ	*p*	η^2p
VO_2max (ml/kg/min)	20.3 (5.1)	26.8 (5.8)	6.5	**<0.001**	0.770	20.4 (5.2)	18.2 (5.4)	-2.2	**0.013**	0.259
Lactate Threshold (W)	71.0 (22.2)	87.1 (23.6)	16.1	**<0.001**	0.499	87.2 (31.7)	83.2 (25.2)	-4.0	0.289	0.053
Ventilatory Threshold (%VO_2max)	49.7 (9.3)	64.2 (11.2)	14.5	**<0.001**	0.558	59.4 (15.0)	58.2 (15.8)	-1.2	0.682	0.008
Power Output (W)	95.0 (27.6)	110.0 (29.2)	15.0	**<0.001**	0.597	102.3 (37.8)	96.8 (30.7)	-5.5	0.066	0.152

Data expressed as mean (SD). VO_2max: maximum oxygen uptake; W: watts.

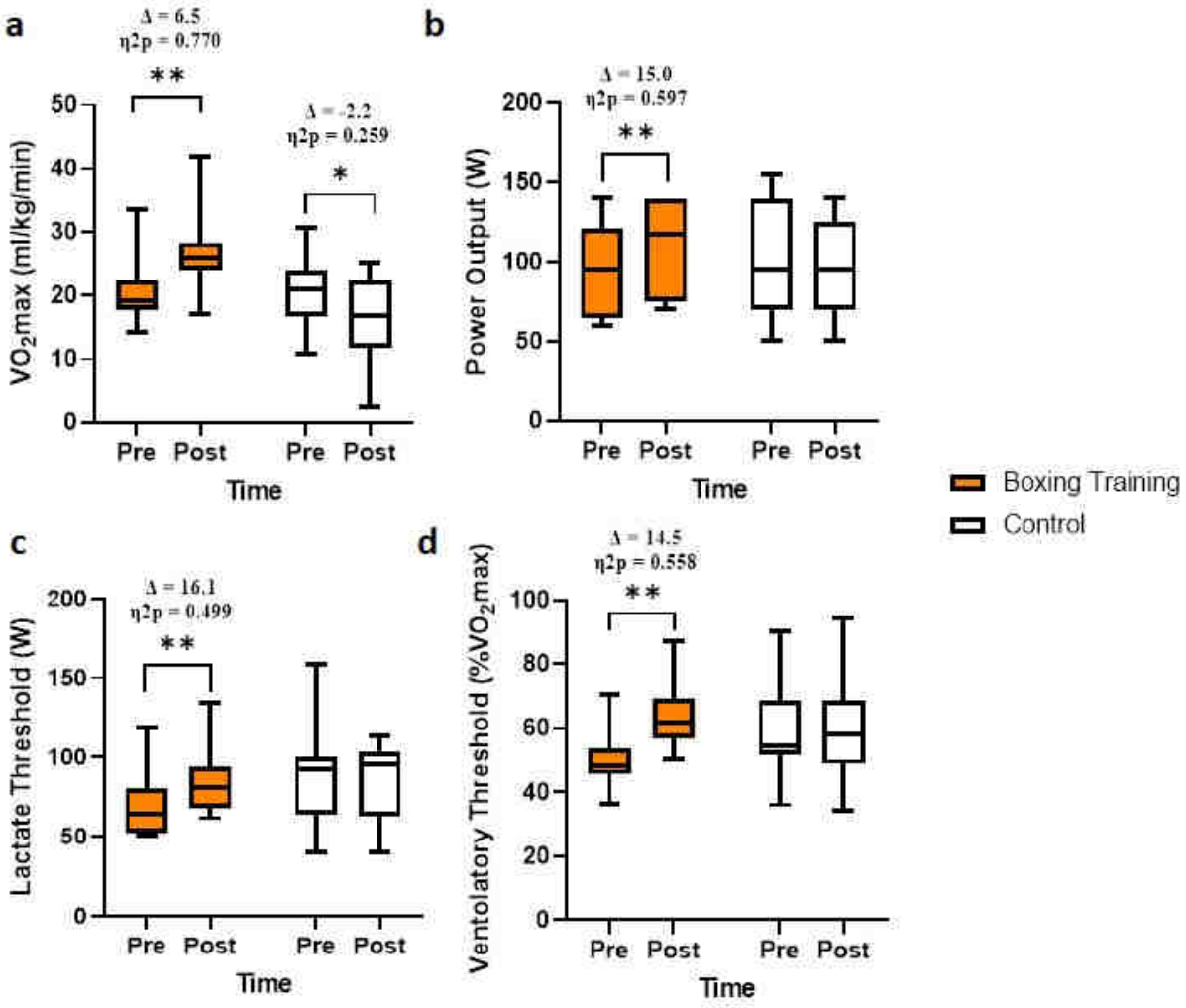

Figure 10. Box plots of exercise capacity changes after boxing training. a) Maximum oxygen uptake (VO_2max); b) Power Output; c) Lactate Threshold; d) Ventilatory Threshold. ** $p < 0.01$, * $p < 0.05$.

4.1.6. Cardiac Adaptations

Significant group x time interactions were observed for resting heart rate ($F(1,21) = 22.60$, $p < 0.001$). No differences were observed in heart rate between groups at baseline ($F(1,21) = 0.02$, $p = 0.890$). Six weeks of boxing training largely decreased resting heart rate ($F(1,21) = 32.81$, $p < 0.001$, $\eta_p^2 = 0.610$) in individuals with elevated blood pressure and stage 1 hypertension. Additionally, there was a significant reduction in resting heart rate ($F(1,21) = 11.79$, $p = 0.002$, $\eta_p^2 = 0.360$) after the intervention in the boxing group compared to the control group. No differences were found before and after the intervention in the control group regarding resting heart rate ($F(1,21) = 1.20$, $p = 0.285$, $\eta_p^2 = 0.054$) (Figure 11).

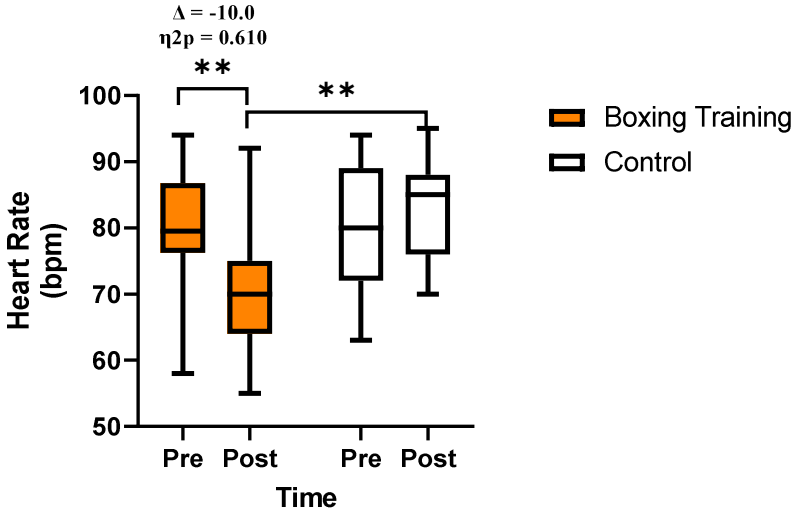

Figure 11. Box plots of heart rate changes after boxing training; bpm: beats per minute. ** $p < 0.01$

There were no significant group x time interactions for aortic size ($F(1,18) < 0.01$, $p = 0.969$), interventricular septum thickness ($F(1,18) = 0.09$, $p = 0.764$), left ventricle end diastolic dimension ($F(1,18) = 0.27$, $p = 0.612$), posterior wall thickness ($F(1,18) = 2.17$, $p = 0.158$), ejection fraction ($F(1,18) = 0.010$, $p = 0.762$), left ventricle mass ($F(1,18) = 0.91$, $p = 0.352$), end diastolic volume ($F(1,18) = 0.73$, $p = 0.405$), stroke volume ($F(1,18) = 0.01$, $p = 0.907$), and lateral tissue doppler imaging (e': $F(1,18) = 0.31$, $p = 0.586$; a': $F(1,18) = 0.37$, $p = 0.551$) However, there was a significant group effect for ejection fraction ($F(1,18) = 4.65$, $p = 0.045$) (Table 8). A lower ejection fraction value was observed in the control group compared to the boxing group at the post assessment ($F(1,18) = 4.80$, $p = 0.042$, $\eta_p^2 = 0.211$). No differences were observed in aortic size ($F(1,18) < 0.01$, $p = 0.777$), interventricular septum thickness ($F(1,18) < 0.01$, $p = 0.985$), left ventricle end diastolic dimension ($F(1,18) = 0.30$, $p = 0.591$), posterior wall thickness ($F(1,18) = 1.31$, $p = 0.268$), ejection fraction ($F(1,18) = 3.60$, $p = 0.074$), left ventricle mass ($F(1,18) = 1.31$, $p = 0.268$), end diastolic volume ($F(1,18) = 0.19$, $p = 0.671$), stroke volume ($F(1,18) = 1.34$, $p = 0.262$), and lateral tissue doppler imaging (e': $F(1,21) < 0.01$, $p = 0.949$; a': $F(1,21) = 0.37$, $p = 0.553$) between groups at baseline.

Table 8. Echocardiographic characteristics before and after 6 weeks intervention.

	Boxing Training			Control			Interaction	Group	Time
	Before	After	Δ	Before	After	Δ	*p*	*p*	*p*
Ao SV (mm)	29.5 (1.7)	29.3 (1.6)	-0.2	29.2 (2.4)	29.3 (1.6)	0.1	0.969	0.767	0.42
IVSd (mm)	9.2 (1.5)	9.4 (1.5)	0.2	9.2 (0.7)	9.3 (0.7)	0.1	0.764	0.977	0.047
LVEDD (mm)	42.6 (6.1)	42.3 (5.5)	-0.3	41.1 (5.6)	40.4 (5.8)	-0.7	0.612	0.513	0.288
PWd (mm)	9.5 (1.5)	9.0 (1.6)	-0.5	8.8 (1.3)	8.7 (1.3)	-0.1	0.158	0.414	0.054
LV EF (%)	61.8 (7.0)	61.6 (6.9)	-0.2	56.0 (6.6)	55.2 (6.1)	-0.8	0.762	**0.045**	0.614
LV Mass (g)	133.8 (41.4)	127.6 (46.2)	-6.2	116.7 (32.2)	114.6 (31.2)	-2.1	0.352	0.387	0.069
LV EDV (ml)	108.5 (26.0)	112.9 (33.3)	4.4	103.5 (25.4)	101.1 (24.6)	-2.4	0.405	0.480	0.802
SV (ml)	57.6 (12.0)	58.6 (18.7)	1.0	49.3 (19.1)	50.7 (18.4)	1.4	0.907	0.298	0.537
Lat e' (cm/s)	13.8 (3.2)	14.9 (3.5)	1.1	13.9 (3.6)	14.5 (3.4)	0.6	0.586	0.920	0.076
Lat a' (cm/s)	6.7 (1.4)	6.4 (1.4)	-0.3	7.2 (2.2)	7.3 (2.0)	0.1	0.551	0.342	0.765

Data expressed as mean (SD). Ao SV: aortic diameter at sinus of Valsalva; IVSd: end-diastolic interventricular septum thickness; LVEDd: left ventricular end diastolic internal diameter; PWd, left ventricular end-diastolic posterior wall thickness; LV EF: left ventricle ejection fraction; EDV: end-diastolic volume; SV: stroke volume.

4.1.7. Body Composition

Significant group x time interactions were observed for weight ($F(1,21) = 4.38$, $p = 0.049$) and BMI ($F(1,21) = 4.86$, $p = 0.039$). There were medium weight ($F(1,18) = 5.53$, $p = 0.029$, $\eta_p^2 = 0.209$) and BMI ($F(1,18) = 5.12$, $p = 0.034$, $\eta_p^2 = 0.196$) gains in the control group. There were no significant group x time interactions for %BF ($F(1,21) = 0.04$, $p = 0.846$), fat mass ($F(1,21) = 2.32$, $p = 0.142$), lean mass ($F(1,21) = 0.27$, $p = 0.611$), free fat mass ($F(1,21) =$

0.26, p = 0.614), bone mineral content (F(1,21) = 0.02, p = 0.899), and bone mineral density (F(1,21) = 0.01, p = 0.934) (Table 9). No differences were observed in weight (F(1,21) = 0.61, p = 0.442), BMI (F(1,21) = 0.57, p = 0.459), %BF (F(1,21) = 0.32, p = 0.575), fat mass (F(1,21) = 0.54, p = 0.469), lean mass (F(1,21) = 0.17, p = 0.685), free fat mass (F(1,21) = 0.17, p = 0.682), bone mineral content (F(1,21) = 0.25, p = 0.623), and bone mineral density (F(1,21) = 0.48, p = 0.496) between groups at baseline.

Table 9. Anthropometric and body composition changes following 6 weeks of intervention.

	Boxing Training			Control			Interaction	Group	Time
	Before	After	Δ	Before	After	Δ	*p*	*p*	*p*
Weight (kg)	89.3 (25.2)	89.0 (26.0)	-0.3	96.3 (16.4)	97.3 (17.0)	1.0	**0.049**	0.409	0.206
BMI	32.3 (7.8)	32.1 (8.1)	-0.2	34.5 (6.0)	34.9 (6.2)	0.4	**0.039**	0.417	0.300
Body Fat %	37.9 (12.3)	38.1 (12.1)	0.2	40.5 (6.4)	40.9 (9.0)	0.4	0.846	0.564	0.149
Fat Mass (kg)	33.4 (16.6)	33.4 (16.4)	0	38.0 (12.9)	38.7 (13.0)	0.7	0.142	0.438	0.093
Lean Mass (kg)	52.5 (13.6)	52.3 (14.1)	-0.2	54.5 (9.6)	54.7 (9.4)	0.2	0.611	0.664	0.94
Free Fat Mass (kg)	55.4 (14.1)	55.2 (14.7)	-0.2	57.5 (10.0)	57.7 (9.7)	0.2	0.614	0.661	0.936
Bone Mineral Content (kg)	2.9 (0.6)	2.9 (0.6)	0	3.0 (0.5)	3.0 (0.5)	0	0.899	0.62	0.886
Bone Mineral Density (gr/cm^2)	1.3 (0.1)	1.3 (0.2)	0	1.3 (0.1)	1.3 (0.1)	0	0.934	0.514	0.240

Data expressed as mean (SD).

4.1.8. Lipid Profile

There were no significant group x time interactions for HDL-C ($F(1,20) = 0.82$, $p = 0.376$), LDL-C ($F(1,20) = 0.02$, $p = 0.894$), and total cholesterol ($F(1,20) = 0.93$, $p = 0.347$) (Table 10). No differences were observed in HDL-C ($F(1,20) = 0.32$, $p = 0.576$), LDL-C ($F(1,20) = 0.31$, $p = 0.581$), and total cholesterol ($F(1,20) = 1.79$, $p = 0.196$) between groups at baseline.

Table 10. Lipid profile changes following 6 weeks of intervention.

	Boxing Training			Control			Interaction	Group	Time
	Before	After	Δ	Before	After	Δ	*p*	*p*	*p*
HDL-C (mg/dl)	42.6 (11.4)	41.2 (13.0)	-1.4	45.3 (10.5)	47.2 (9.0)	1.9	0.376	0.332	0.905
LDL-C (mg/dl)	56.7 (1.8)	57.5 (2.1)	0.8	56.2 (2.6)	56.8 (2.1)	0.6	0.894	0.494	0.074
Total Cholesterol (mg/dl)	132.0 (4.6)	132.0 (5.7)	0	134.7 (4.8)	131.9 (3.9)	-2.8	0.347	0.383	0.337

Data expressed as mean (SD). HDL-C: high density lipoprotein; LDL-C: low density lipoprotein.

4.1.9. Quality of Life

Significant group x time interactions were observed for role limitations due physical health problems ($F(1,21) = 10.02$, $p = 0.003$), role limitations due emotional problems ($F(1,21) = 4.19$, $p = 0.05$), and general health ($F(1,21) = 8.30$, $p = 0.009$). A large increase in general health ($F(1,21) = 13.54$, $p = 0.001$ $\eta_p^2 = 0.392$) was observed in the boxing group after the intervention. Large reductions in role limitations due physical health problems ($F(1,21) = 8.71$, $p = 0.008$, $\eta_p^2 = 0.293$) and role limitations due emotional problems ($F(1,21) = 11.19$, $p = 0.003$, $\eta_p^2 = 0.348$) were observed in the control group at the end of the intervention. There were a significant group effects for vitality ($F(1,21) = 5.74$, $p = 0.026$) and mental health ($F(1,21) = 7.95$, $p = 0.01$)

(Table 11). Lower scores in vitality (F(1,21) = 7.80, p = 0.011, η_p^2 = 0.271) and mental health (F(1,21) = 9.11, p = 0.007, η_p^2 = 0.303) were observed in the boxing group compared to the control group at the post assessments. No differences were observed in physical functioning (F(1,21) = 0.90, p = 0.767), role limitations due emotional problems (F(1,21) = 0.11, p = 0.749), vitality (F(1,21) = 2.57, p = 0.124), social functioning (F(1,21) = 0.75, p = 0.397), bodily pain (F(1,21) = 0.28, p = 0.606), and general health (F(1,21) = 0.67, p = 0.434) between groups at baseline. Meanwhile, there were differences in role limitations due physical health problems (F(1,21) = 4.60, p = 0.044) and mental health (F(1,21) = 4.81, p = 0.040) between groups at baseline.

Table 11. Quality of life changes following 6 weeks of intervention.

	Boxing Training			Control			Interaction	Group	Time
	Before	After	Δ	Before	After	Δ	*p*	*p*	*p*
Physical Functioning (%)	81.7 (25.2)	89.2 (24.6)	7.5	84.6 (20.1)	81.0 (20.4)	-3.6	0.082	0.768	0.533
Role limitation Physical (%)	85.4 (22.5)	97.9 (7.2)	12.5	100 (0)	77.3 (30.5)	-22.7	**0.003**	0.618	0.348
Role limitation Emotional (%)	77.8 (41.0)	72.2 (44.5)	-5.6	72.7 (32.7)	36.4 (27.7)	-36.3	**0.050**	0.149	0.011
Vitality (%)	60.0 (17.7)	66.7 (22.1)	6.7	49.6 (12.9)	46.4 (9.8)	-3.2	0.067	**0.026**	0.502
Mental Health (%)	73.7 (19.4)	76.3 (21.9)	2.6	58.2 (13.7)	54.2 (10.9)	-4.0	0.232	**0.010**	0.808
Social Functioning (%)	78.1 (22.1)	86.5 (18.0)	8.4	70.5 (20.4)	68.2 (18.0)	-2.3	0.272	0.068	0.527
Bodily Pain (%)	89.4 (18.5)	92.7 (8.7)	3.3	85.5 (17.2)	77.5 (17.7)	-8	0.098	0.115	0.486
General Health (%)	53.8 (24.7)	63.3 (22.5)	9.5	49.1 (18.7)	52.7 (16.5)	3.6	**0.009**	0.362	0.039

Data expressed as mean (SD).

4.1.10. Vascular Adaptations

There was a significant group x time interaction for brachial FMD ($F(1,21) = 22.46$, $p < 0.001$). No differences were observed in brachial artery diameter ($F(1,21) = 0.33$, $p = 0.573$), resting brachial ESS ($F(1,21) < 0.01$, $p = 0.967$), and brachial FMD ($F(1,21) = 0.03$, $p = 0.858$) between groups at baseline. Six weeks of boxing training largely increased brachial FMD ($F(1,21) = 23.58$, $p < 0.001$, $\eta_p^2 = 0.529$) in individuals with elevated blood pressure or stage 1 hypertension. There were no significant group x time interactions for brachial artery diameter ($F(1,21) = 3.05$, $p = 0.095$) and resting brachial ESS ($F(1,21) = 0.75$, $p = 0.398$) (Table 12 and Figure 12).

Significant group x time interactions were observed for popliteal artery diameter ($F(1,14) = 7.74$, $p = 0.015$) and popliteal FMD ($F(1,14) = 18.39$, $p = 0.001$). No differences were observed in popliteal artery diameter ($F(1,14) = 3.90$, $p = 0.068$), resting popliteal ESS ($F(1,14) = 1.35$, $p = 0.264$), and popliteal FMD ($F(1,14) = 0.03$, $p = 0.858$) between groups at baseline. Six weeks of boxing training induced a large increase in popliteal artery FMD ($F(1,14) = 20.19$, $p = 0.001$, $\eta_p^2 = 0.591$) and popliteal artery diameter ($F(1,14) = 7.53$, $p = 0.016$, $\eta_p^2 = 0.350$). There was no group x time interaction for resting popliteal ESS ($F(1,14) = 0.92$, $p = 0.354$) (Table 12 and Figure 13).

There was a significant group x time interaction for carotid artery diameter ($F(1,21) = 13.44$, $p = 0.001$). No differences were observed in carotid artery diameter ($F(1,21) = 3.43$, $p = 0.078$) and resting carotid ESS ($F(1,21) = 0.10$, $p = 0.750$) between groups at baseline. A large increase in carotid artery diameter ($F(1,21) = 11.68$, $p = 0.003$, $\eta_p^2 = 0.357$) was observed in the boxing group at the end of the intervention. There was no group x time interaction for resting carotid ESS ($F(1,21) = 1.55$, $p = 0.228$) (Table 12 and Figure 14).

Table 12. Vascular changes following 6 weeks of intervention.

	Boxing Training			Control			Interaction	Group	Time
	Before	After	Δ	Before	After	Δ	*p*	*p*	*p*
Brachial Diameter (mm)	3.7 (0.6)	3.8 (0.7)	0.1	3.9 (0.6)	3.8 (0.7)	-0.1	0.095	0.881	0.895
Resting Brachial ESS (dynes/cm^2)	31.7 (6.2)	30.0 (6.9)	-1.7	31.6 (6.4)	28.1 (5.1)	-3.5	0.398	0.674	0.022
Brachial FMD (%)	8.5 (4.8)	11.5 (5.4)	3.0	8.2 (3.4)	7.0 (3.6)	-1.2	**<0.001**	0.191	0.061
Popliteal Diameter (mm)	5.6 (1.1)	5.8 (1.1)	0.2	6.6 (1.0)	6.5 (0.9)	-0.1	**0.015**	0.108	0.411
Resting Popliteal ESS (dynes/cm^2)	19.3 (3.0)	20.5 (3.0)	1.2	22.2 (6.6)	21.6 (4.6)	-0.6	0.354	0.336	0.760
Popliteal FMD (%)	8.4 (2.6)	11.0 (3.3)	2.6	8.2 (5.0)	7.0 (4.2)	-1.2	**0.001**	0.265	0.12
Carotid Diameter (mm)	6.7 (0.6)	7.0 (0.6)	0.3	7.2 (0.5)	7.0 (0.6)	-0.2	**0.001**	0.348	0.301
Resting Carotid ESS (dynes/cm^2)	32.4 (5.3)	34.4 (5.9)	2.0	33.3 (7.5)	32.6 (6.6)	-0.7	0.228	0.836	0.572
VOP Forearm Basal (ml/min/100 ml tissue)	2.6 (0.8)	3.3 (1.0)	0.7	3.3 (0.9)	3.2 (1.1)	-0.1	**0.003**	0.469	0.019
VOP Forearm Peak (ml/min/100 ml tissue)	17.1 (4.5)	20.9 (5.7)	3.8	14.9 (3.9)	14.8 (3.9)	-0.1	**<0.001**	0.037	<0.001
VOP Calf Basal (ml/min/100 ml tissue)	2.7 (0.5)	3.0 (0.5)	0.3	3.2 (0.6)	3.2 (0.6)	0	0.134	0.143	0.126
VOP Calf Peak (ml/min/100 ml tissue)	17.6 (4.3)	22.1 (6.2)	4.5	17.4 (6.9)	17.4 (6.2)	0	**0.005**	0.305	0.005

Data expressed as mean (SD). ESS: endothelial shear stress; VOP: venous occlusion plethysmography.

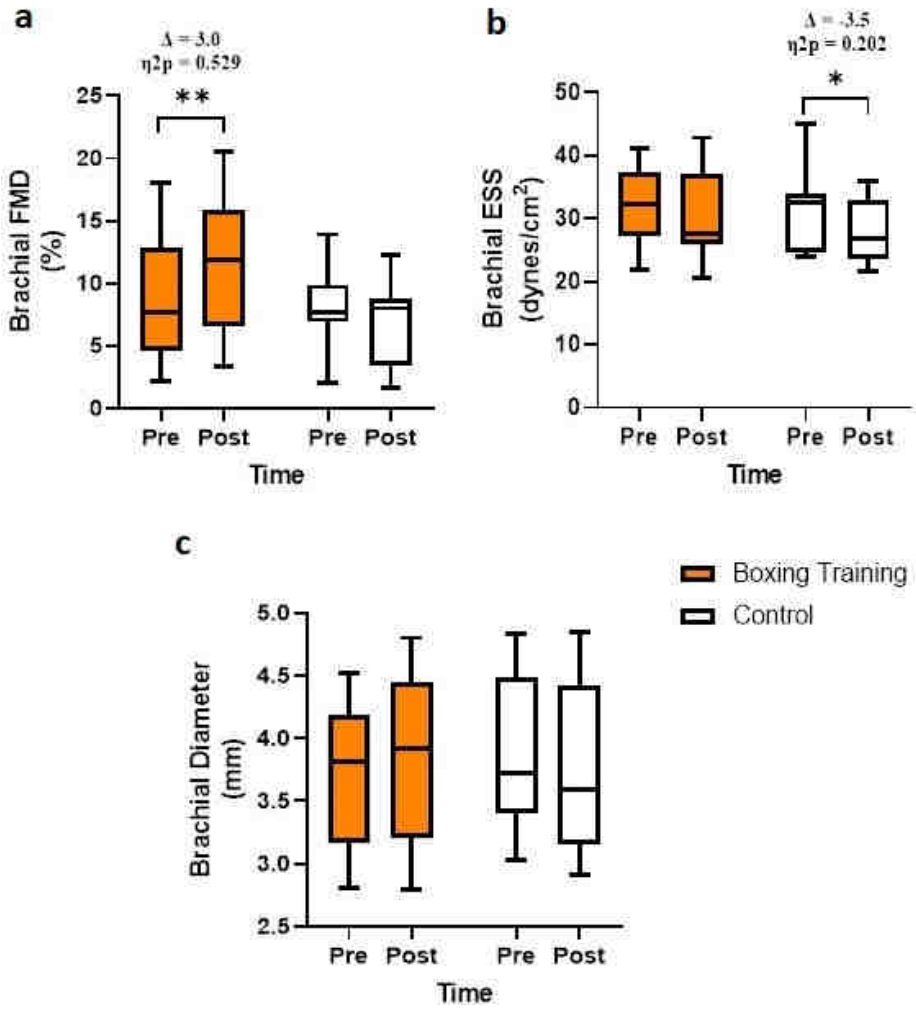

Figure 12. Box plots of brachial artery changes after boxing training. a) Flow-Mediated Dilation (FMD); b) Resting Endothelial Shear Stress (ESS); c) Brachial Artery Diameter. ** $p < 0.01$, *$p < 0.05$

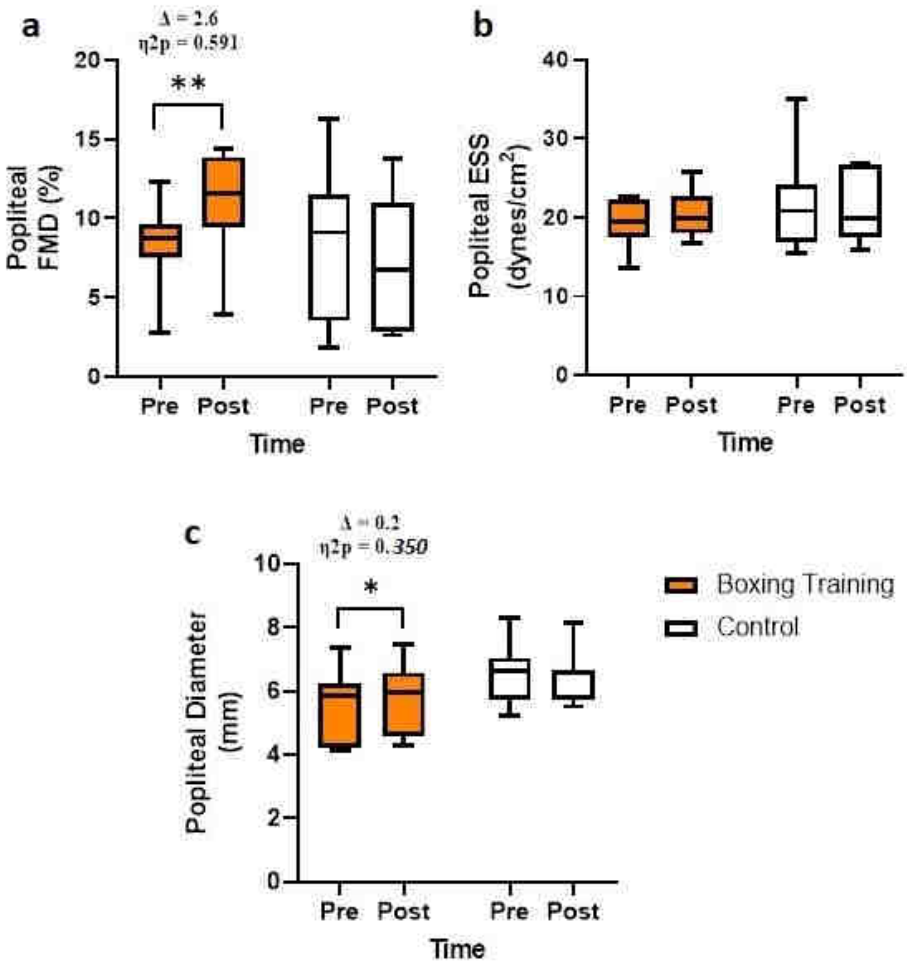

Figure 13. Box plots of popliteal artery changes following boxing training. a) Flow-Mediated Dilation (FMD); b) Resting Endothelial Shear Stress (ESS); c) Artery Diameter. ** p < 0.01, *p < 0.05

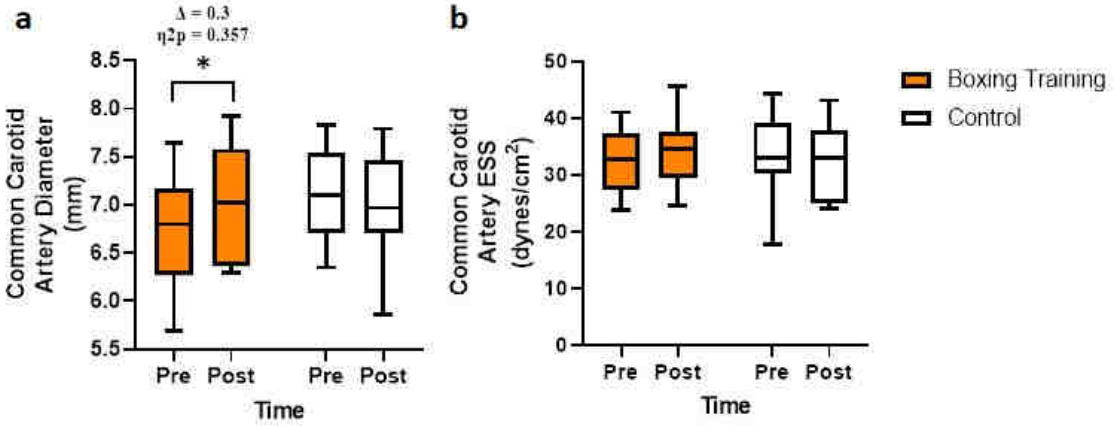

Figure 14. Box plots of common carotid artery changes following boxing training. a) Artery diameter; b) Resting Endothelial Shear Stress (ESS). *p < 0.05

There were significant group x time interactions for basal forearm blood flow ($F(1,21) = 10.88$, $p = 0.003$), peak forearm blood flow ($F(1,21) = 20.17$, $p < 0.001$), and peak calf blood flow ($F(1,21) = 9.71$, $p = 0.005$). No differences were observed in basal forearm blood flow ($F(1,21) = 3.70$, $p = 0.068$), peak forearm blood flow ($F(1,21) = 1.53$, $p = 0.230$), and peak calf blood flow ($F(1,21) = 0.01$, $p = 0.912$), while differences were found in basal calf blood flow ($F(1,21) = 4.58$, $p = 0.044$) between groups at baseline. Six weeks of boxing training led to a large increase in basal forearm blood flow ($F(1,21) = 17.79$, $p < 0.001$, $\eta_p^2 = 0.459$), peak forearm blood flow ($F(1,21) = 39.94$, $p < 0.001$, $\eta_p^2 = 0.655$), and peak calf blood flow ($F(1,21) = 20.58$, $p < 0.001$, $\eta_p^2 = 0.495$) (Figure 15 and Table 12).

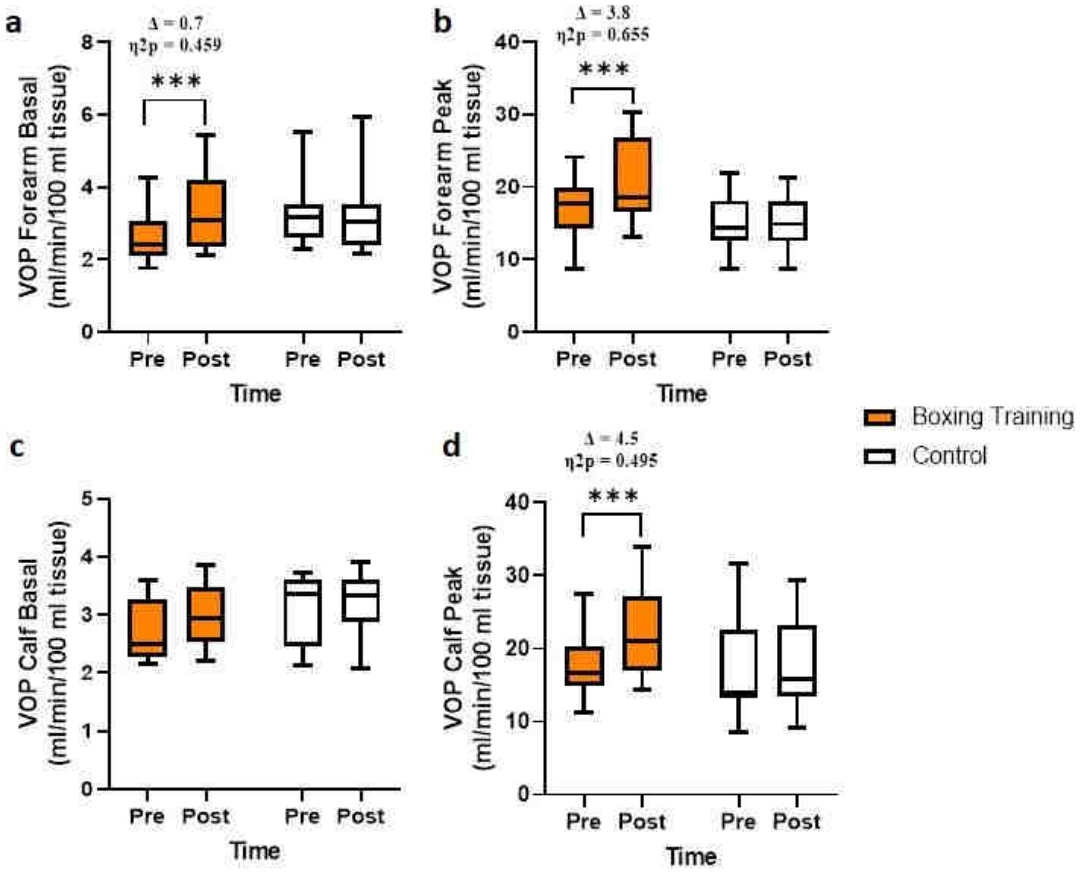

Figure 15. Box plots of venous occlusion plethysmography (VOP) of resistance vessels changes following boxing training. a) Forearm basal flow; b) Forearm peak flow; c) Calf basal flow; d) Calf peak flow. *** $p < 0.001$.

4.1.11. Nitric Oxide Bioavailability

A significant group x time interaction was observed for NOx ($F(1,20) = 10.08$, $p = 0.005$). NOx was similar between groups at baseline ($F(1,20) = 0.67$, $p = 0.424$). A large increase in NOx ($F(1,20) = 8.37$, $p = 0.009$, $\eta_p^2 = 0.295$) was found in the boxing group at the end of the intervention (Figure 16 and Table 13).

Table 13. Blood biomarkers changes following 6 weeks of intervention.

	Boxing Training			Control			Interaction	Group	Time
	Before	After	Δ	Before	After	Δ	*p*	*p*	*p*
NOx (µmol/L)	53.9 (19.6)	68.4 (23.3)	14.5	60.7 (19.9)	52.7 (26.5)	-8	**0.005**	0.627	0.370
CRP (mg/L)	9.1 (7.3)	5.9 (5.1)	-3.2	6.3 (4.4)	6.6 (4.6)	0.3	**0.010**	0.643	0.028
IL-6 (pg/ml)	19.1 (18.3)	19.0 (15.3)	-0.1	15.3 (13.8)	14.7 (14.9)	-0.6	0.851	0.546	0.810
TNFα (pg/ml)	126.9 (185.7)	134.2 (183.6)	7.3	91.4 (138.5)	81.1 (139.7)	-10.3	0.203	0.605	0.244
8-isoprostane (pg/ml)	465.1 (108.0)	487.3 (139.7)	22.2	440.2 (142.2)	535.7 (159.2)	95.5	0.364	0.792	0.152
SOD (mU/ml)	44.5 (6.2)	44.7 (6.4)	0.2	43.7 (6.5)	43.5 (6.9)	-0.2	0.731	0.710	1.000
TAC (mM/ml)	5.6 (2.5)	6.8 (3.5)	1.2	5.2 (2.7)	4.8 (2.0)	-0.4	0.151	0.242	0.408

Data expressed as mean (SD). NOx: nitric oxide; CRP: c-reactive protein; IL: interleukin; SOD: superoxide dismutase; TAC: total antioxidant capacity.

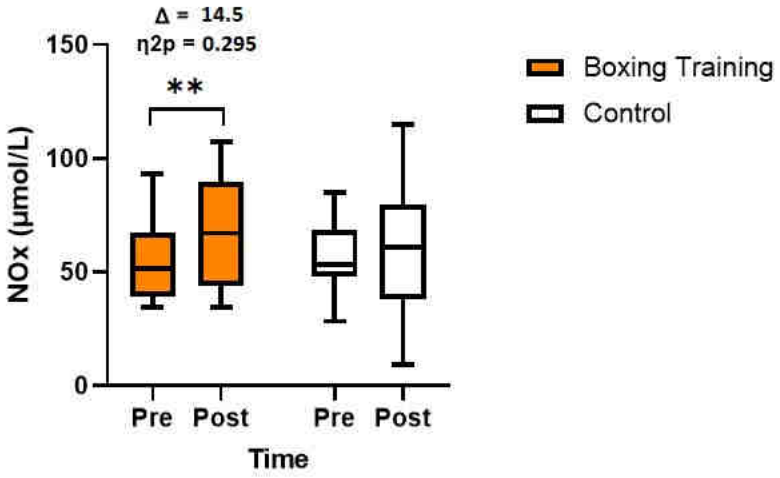

Figure 16. Box plots of Nitric Oxide changes after the intervention. * $p < 0.05$.

4.1.12. Inflammation

A significant group x time interaction was observed for CRP ($F(1,20) = 8.03$, $p = 0.01$). No differences were observed in CRP ($F(1,20) = 0.11$, $p = 0.745$), IL-6 ($F(1,20) = 0.30$, $p = 0.593$), and TNF-α ($F(1,18) = 0.23$, $p = 0.641$) between groups at baseline. Six weeks of boxing training largely reduced CRP ($F(1,20) = 13.53$, $p = 0.001$, $\eta_p^2 = 0.404$) (Figure 17 and Table 13). A significant group x time interaction was also found for CRP ($F(1,14) = 6.37$, $p = 0.024$) when CRP values >10 mg/L in the pre assessment were excluded (Appendix B). There were no significant group x time interactions for IL-6 ($F(1,20) = 0.36$, $p = 0.851$) and TNF- α ($F(1,20) = 1.74$, $p = 0.203$) (Table 13).

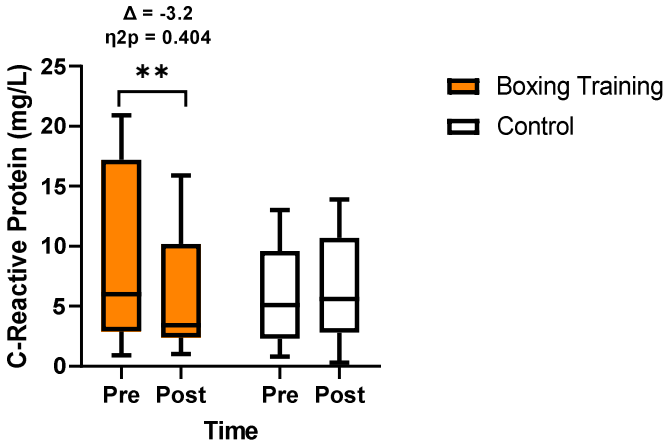

Figure 17. Box plots of C-Reactive Protein changes after the intervention. ** $p < 0.01$.

4.1.13. Oxidative Stress

There were no group x time interactions for 8-isoprostane ($F(1,20) = 0.86$, $p = 0.364$), SOD ($F(1,20) = 0.12$, $p = 0.731$), and TAC ($F(1,20) = 2.23$, $p = 0.151$) (Table 13). No differences were observed in 8-isoprostane ($F(1,20) = 0.21$, $p = 0.649$), SOD ($F(1,20) = 0.07$, $p = 0.791$), and TAC ($F(1,20) = 0.16$, $p = 0.693$) between groups at baseline.

4.2. Experiment 2: Cross Sectional Study

A total of 10 participants (7 males and 3 females) with elevated blood pressure or stage 1 hypertension were recruited for the present study. Data was normally distributed and was presented as mean (standard deviation). Demographic characteristics are display in Table 14.

Table 14. Demographic characteristics of the participants.

	N = 10
Age (y)	24.7 (4.2)
Height (m)	1.7 (0.1)
Weight (kg)	72.5 (13.0)
Hematocrit (%)	48.7 (2.5)
SBP (mmHg)	127.4 (4.6)
DBP (mmHg)	79.1 (5.0)

Data expressed as mean (SD). SBP: systolic blood pressure; DBP: diastolic blood pressure.

Heart rate, VO_2, lactate, and RPE were significantly increased during both exercise conditions (all $p < 0.001$) in comparison to baseline. Also, all these exercise variables were higher at 95%VO_2max in comparison to 60%VO_2max (all $p < 0.001$) (Table 15).

Table 15. Exercise variables during boxing training

N = 10	Baseline	60%VO_2max	95%VO_2max
Heart Rate (bpm)	68.8 (11.7)	129.0 (12.5)*	164.7 (18.3)*&
VO_2 (ml/kg/min)	3.5 (0.7)	12.9 (2.8)*	21.3 (5.0)*&
Lactate (mmol/L)	0.8 (0.4)	2.4 (0.6)*	5.2 (1.3)*&
RPE (6-20)	0	10.7 (2.5)*	15.9 (2.8)*&
ESS Anterograde (dynes/cm^2)	32.6 (8.9)	47.2 (11.3)*	77.4 (17.2)*&
ESS Retrograde (dynes/cm^2)	0	6.9 (4.5)*	19.5 (10.2)*&

Data expressed as mean (SD). VO_2: oxygen uptake; RPE: rate of perceive exertion; ESS: endothelial shear stress.
** = $p < 0.05$ vs Baseline; *& = $p < 0.05$ vs 60%VO_2max.*

There was a large significant increase in anterograde ESS during boxing training at both intensities in comparison to resting conditions ($p < 0.05$, $d = 1.44 – 3.27$). Additionally, there was a large increase in anterograde ESS at 95%VO_2max in comparison to ESS at 60%VO_2max ($p < 0.001$, $d = 2.08$) (Figure 18).

Retrograde ESS followed the same trend as anterograde ESS. There was a large increase in retrograde ESS at both exercise conditions in comparison to baseline ($p < 0.05$, $d = 2.17 – 4.00$), while a large increase in retrograde ESS was observed at 95%VO_2max in comparison to ESS at 60%VO_2max ($p < 0.001$, $d = 2.16$) (Figure 18).

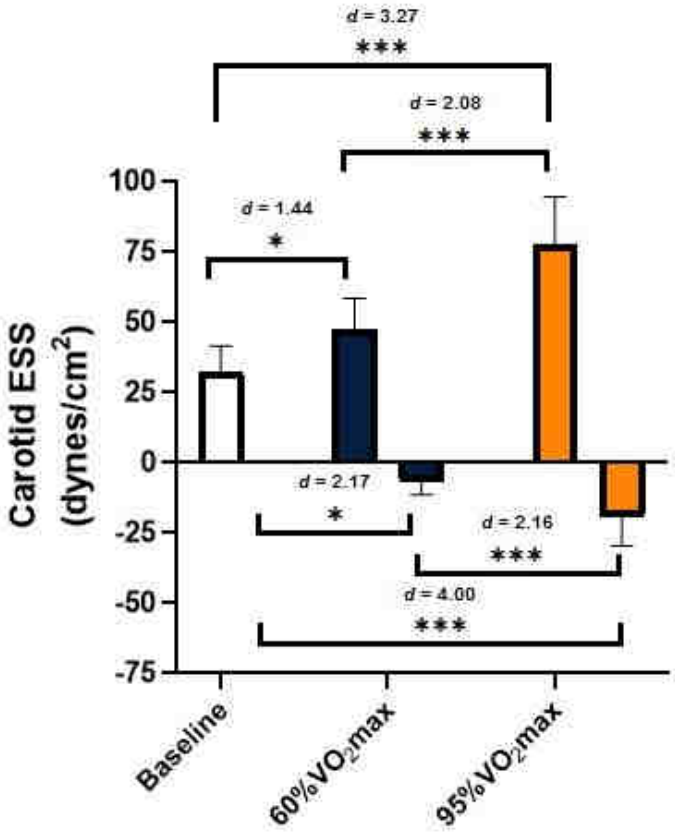

Figure 18. Carotid artery endothelial shear stress (ESS) during boxing training at 60%VO_2max and 95%VO_2max. *** $p < 0.001$.

Anterograde blood flow patterns were turbulent at baseline and during both exercise conditions. Meanwhile, retrograde blood flow patterns were laminar at 60%VO_2max and there was a tendency to become turbulent at 95%VO_2max (Figure 19).

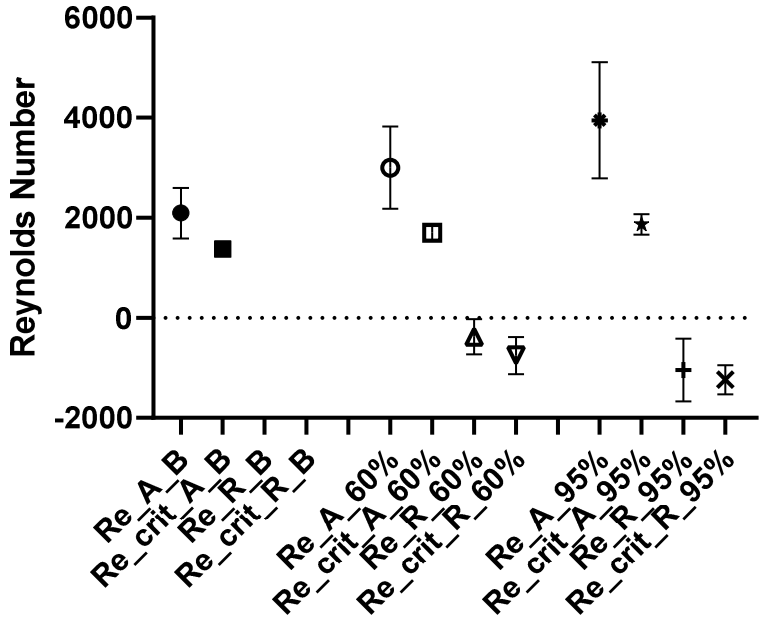

Figure 19. Blood flow patterns in the common carotid artery during boxing training at 60%VO_2max and 95%VO_2max.

CHAPTER 5: DISCUSSION

The present study is the first randomized controlled trial to evaluate the effects of boxing training on brachial blood pressure, central blood pressure, arterial stiffness, exercise capacity, cardiac adaptations, body composition, lipid profile, quality of life, vascular adaptations, nitric oxide bioavailability, inflammation, and oxidative stress in individuals with elevated blood pressure or stage 1 hypertension. The main findings we identified were that 6 weeks of boxing training with a polarized intensity regime in individuals with elevated blood pressure or stage 1 hypertension improves: (1) clinical outcomes, such as peripheral and central blood pressure, resting heart rate, VO_2max, ventilatory and lactate thresholds, and quality of life, and (2) vascular outcomes, specifically, improving conduit artery endothelial function, resistance vessels structure and endothelial function, and carotid artery structure, all changes linked to an increase in NO bioavailability and a decrease in inflammation. Additionally, the present study is the first one to assess blood flow changes in the carotid artery during a novel exercise modality and to determine that ESS and blood flow patterns during boxing training, may be involved with structural or functional adaptations in the vasculature of individuals with elevated blood pressure or stage 1 hypertension.

5.1. Boxing Training

To the best of our knowledge, this is the first study to evaluate the effects of boxing training on cardiovascular health in individuals with elevated blood pressure or stage 1 hypertension. The boxing training regimen consisted of ~43 minutes workouts (3-minute warm up and 10 rounds of 3-minute punching interspersed with 1-minute passive resting) on 3 non-consecutive days per week for 6 weeks. The intensity of each session had a polarized design,

where 30% and 70% of the time corresponded to high- and low-intensity exercise, respectively. The high compliance to the exercise sessions observed in the present study (98.1%) suggest that this approach is suitable for physically inactive individuals and for beginners in boxing training. In addition, the compliance to boxing training from the present study was superior to the one described by the Cheema et al. [52] study (~79%). These differences may be explained by the characteristics of the present boxing training program, which may be more appealing to physically inactive individuals compared to the Cheema et al. program specifically due to the intensity (Polarized versus HIIT) and duration (6 weeks versus 12 weeks).

Polarized training has been shown to be very successful for improving performance in athletes [310-314]; however, there is limited research on the effectiveness of polarized training on clinical outcomes in the CVD population. In an elegant study, Zapata-Laman et al. [146] compared the effects of 12-week polarized training, moderate-intensity training, or HIIT on cardiometabolic risk in young overweight and obese women. They found that polarized training had superior effects on exercise capacity, glycemic control, and substrate oxidation in comparison to the other training modalities. These findings suggest that polarized training is an appropriate approach to control cardiovascular risk factors in CVD population.

In the present study, no cardiovascular adverse events were detected. However, 25% of the participants experienced self-limiting shoulder pain when punching during their first week of training, which subsided during the second week and no further pain was reported. Thus, boxing training can still be considered safe in individuals with elevated blood pressure or stage 1 hypertension. Caution should be taken in using boxing training in individuals who have a pre-existing shoulder injury (e.g. rotator cuff tendinopathy).

5.2. Clinical Outcomes

5.2.1. Peripheral Blood Pressure

The present study demonstrated that 6 weeks of boxing training induced a large reduction in brachial SBP (~16 mmHg) and DBP (~10 mmHg) in individuals with elevated blood pressure or stage 1 hypertension (Table 5 and Figure 7). Similarly, Cheema et al. [52] reported 14 and 7 mmHg reductions in SBP and DBP, respectively, after 16 weeks of boxing training in adults with abdominal obesity. The findings of the present study are also in agreement with previous meta-analyses studying the effects of exercise in blood pressure. For example, Cornelissen et al. [18] reported an overall reduction in SBP/DBP of 3.5/2.5, 1.8/3.2, and 10.9/6.2 mmHg in endurance, resistance, and isometric training, respectively, in healthy or individuals with high blood pressure. In addition, de Sousa et al. [28] reported 8.3 and 4.1 mmHg reductions in SBP and DBP, respectively, after resistance training in individuals with high blood pressure. Furthermore, Inder et al. [29] reported 5.2 and 3.9 mmHg reductions in SBP and DBP, respectively, after isometric exercise training in healthy or individuals with high blood pressure. Moreover, Williamson et al. [315] reported 4.4 and 4.2 mmHg reductions in SBP and DBP, respectively, after a physical activity intervention in young adults with elevated blood pressure, stage 1 hypertenson, or stage 2 hypertension. The SBP and DBP reductions described in those meta-analyses were lower than the reductions from the present study and the Cheema et al. study. The differences may rely on the intrinsic nature of boxing training, which is a whole-body physical activity but with an upper-body emphasis, that could induce more prominent local changes in the brachial artery (e.g. higher ESS). Also, heterogeneity in the studies that were included in those meta-analyses (e.g. exercise prescription, sample size, adherence) may affect the net observations. Blood pressure reductions following boxing training may be explained, in part, to

an improvement in ESS, NO bioavailability, and endothelial function and a reduction in vascular inflammation and peripheral vascular resistance (Tables 12 and 13).

Lewington et al. [316] reported that a 10 mmHg reduction in SBP results in a 30% decreased risk in coronary artery disease mortality and a 40% decreased risk in stroke mortality. In the same study, Lewington et al. reported that even smaller reductions (~2 mmHg) in SBP results in a 7% and 10% decreased risk in coronary artery disease and stroke mortality, respectively. Additionally, Verdecchia et al. [317] reported that a 2 mmHg reduction in DBP results in a 12% decrease risk of myocardial infarction, stroke, and cardiovascular mortality. Based on these previous findings, the results of the present study are clinically meaningful findings.

5.2.2. Central Blood Pressure

Central hemodynamics represent the pressure in the ascending aorta and downstream (e.g. end-organs). An elevation of the central blood pressure has an adverse effect on the vasculature and on end-organs, especially in the high blood pressure population [318]. Additionally, central blood pressure is recognized as a more powerful maker of end-organ damage and cardiovascular mortality compared to brachial blood pressure [99,319].

In the present study, 6 weeks of boxing training largely reduced cSBP (~8 mmHg) in individuals with elevated blood pressure or stage 1 hypertension (Table 6 and Figure 8). Similar to the findings from the present study, Beck et al. [320] reported a reduction in cSBP after 8 weeks of endurance (~11 mmHg) or resistance training (~10 mmHg) in young individuals with elevated blood pressure or stage 1 hypertension. This finding may be explained by an exercise-induced vasodilatory effect on resistance vessels in individuals with high blood pressure that

reduced the magnitude of reflected pressure waves. Additionally, in the present study, no statistical reductions were observed in AIx or AIx@75 after 6 weeks of boxing training in individuals with elevated blood pressure or stage 1 hypertension (Table 6). Previous studies have reported equivocal findings regarding the effects of exercise on AIx. Cheema et al. [52] reported a reduction in AIx after 16 weeks of boxing training in adults with abdominal obesity. Donley et al. [321] reported a reduction in cSBP and AIx@75 after 8 weeks of endurance training in adults with metabolic syndrome. Krustrup et al. [322] reported reductions in AIx after 12 and 24 weeks of soccer training in males with high blood pressure. Nualnim et al. [243] reported a no significant reduction in AIx after 12 weeks of swimming training in elderly individuals with high blood pressure. Seals et al. [323] reported no changes in AIx after 12 weeks of walking training in elderly women with high blood pressure women. Westhoff et al. [323] reported no changes in AIx and AIx@75 after of upper-body endurance training in elderly individuals with high blood pressure. Lastly, Heffernan et al. [324] reported no changes in AIx following 12 weeks of resistance training in elderly individuals with high blood pressure. These incongruent results may be explained by the heterogenicity in exercise programs and sample characteristics (e.g. age, sex, morbidity) among studies.

Based on the findings of Vlachopoulos et al. [325], who reported that a 10 mmHg reduction in cSBP translates into a 8.8% decrease in the risk for future cardiovascular events, we propose that the findings of the present study are clinically relevant because a mean reduction of ~8 mmHg was observed after 6 weeks of boxing training in individuals with elevated blood pressure or stage 1 hypertension.

Finally, in the present study, a no significant reduction in LVE_W (~37%) was observed after 6 weeks of boxing in individuals with elevated blood pressure or stage 1 hypertension

(Table 6). LVE_W is a relatively new biomarker that describes the additional energy required by the myocardium to overcome the augmented pressure generated by the reflected pressure wave. Thus, reductions in LVE_W may prevent the progression to pathological ventricular hypertrophy secondary to high blood pressure [326]. There are only few studies that have explored the effects of exercise on LVE_W. For example, Beck et al. [320] reported a reduction in LVEw after 8 weeks of endurance (~76%) or resistance training (~82%) in young individuals with elevated blood pressure or stage 1 hypertension. Based on these and the current study results, significant reductions in LVEw might be seeing after longer training periods.

5.2.3. Arterial Stiffness

Large-artery stiffness is an independent risk factor for cardiovascular mortality and it is usually associated with high blood pressure [327]. In fact, it has been proposed that arterial stiffness is a mechanism behind the development or progression of high blood pressure [328,329]. PWVcf is the gold standard to assess arterial stiffness and its reduction is associated to better cardiovascular outcomes [330,331].

In the present study, no changes in PWVcf were observed after 6 weeks of boxing training in individuals with elevated blood pressure and stage 1 hypertension (Figure 9). These findings are in agreement with those of previous studies. Beck et al. [320] reported no changes in PWVcf after 8 weeks of endurance or resistance training in individuals with elevated blood pressure or stage 1 hypertension. Ferrier et al. [332] reported no PWVcf change following 8 weeks of cycling training in individuals with high blood pressure. Seals et al. [323] reported no effects on PWVcf after 12 weeks of endurance training in postmenopausal women with high blood. Stewart et al. [333] reported no significant changes in PWVcf after 24 weeks of

endurance and resistance training in elderly individuals with high blood pressure in comparison to a control group. Lastly, Guimaraes et al. [201] reported a small reduction and no changes in PWVcf after 16 weeks of interval or continuous endurance training in individuals with high blood pressure. In contrast, Madden et al. [334] reported ~3 m/s and ~1 m/s reductions in PWVcf after 12 and 24 weeks of endurance training in individuals with high blood pressure with other cardiovascular comorbidities. Interestingly, Collier et al. [213] reported that 4 weeks of resistance increased PWVcf and 4 weeks of endurance training reduced PWVcf in individuals with high blood pressure. In a recent study, Bhuva et al. [335] reported a reduction in PWV across the length of the whole aorta measured by cardiovascular magnetic resonance after 24 weeks of endurance training in healthy sedentary individuals. Overall, exercise training programs shorter than 6 weeks are less likely to induce structural adaptations in elastic arteries in individuals with high blood pressure.

5.2.4. Cardiorespiratory Fitness

Exercise training has been extensively reported to increase cardiorespiratory fitness [31,336]. In the present study, 6 weeks of boxing training improved upper-body power output (~16%), VO_2max (~32%), and ventilatory (~29%) and lactate (~23%) thresholds in individuals with elevated blood pressure or stage 1 hypertension (Table 7 and Figure 10). The present findings confirm previously reported data regarding improvements in cardiorespiratory fitness through exercise in individuals with CVD. Cheema et al. [52] reported a 16.9% increase in VO_2max after 16 weeks of boxing training in adults with abdominal obesity. Azadpour et al. [337] reported a 22.7% rise in VO_2max after 10 weeks of endurance training in individuals with elevated blood pressure or stage 1 hypertension. Miyatake et al. [338] reported an increase in

exercise performance at the ventilatory threshold and a 12.4% rise in VO_2max after 48 weeks of low-intensity endurance exercise in individuals with high blood pressure and obesity. Moreover, Dimeo et al. [339] reported a right shift in the lactate threshold curve and a 6.6% increase in VO_2max after 8- to 12- weeks of endurance training in individuals with high blood pressure. Improvements in the cardiorespiratory fitness are explained by changes at both central (e.g. maximal cardiac output) and peripheral (e.g. maximal arterial-venous oxygen difference) levels. Approximately two-thirds of the gains are explained by modifications at the central level such as greater stroke volume during exercise due to enhance left ventricular filling and contractility. The remaining third is explained by changes at the peripheral level such as greater capillarization, muscle fibers adaptations, reduced vascular peripheral resistance, improvement in enzymatic activity, and microvascular blood flow distribution [340,341].

5.2.5. Cardiac Adaptations

The present study demonstrated that 6 weeks of boxing training reduced resting heart rate (~10 bpm) in young individuals with elevated blood pressure or stage 1 hypertension (Figure 11). This finding was consistent with those of previous studies. Collier et al. [213] reported a reduction in resting heart rate (~5 bpm) after 4 weeks of endurance training in individuals with high blood pressure. Laterza et al. [200] reported a reduction in resting heart rate (~10 bpm) after 16 weeks of cycling training in never-treated hypertensive patients. Lamina et al. [189] reported a reduction in heart rate (~10 bpm) after 8 weeks of cycling training in individuals with high blood pressure.

In the present study, no changes in cardiac structure or diastolic function were observed after 6 weeks of boxing training in young individuals with elevated blood pressure or stage 1

hypertension (Table 8). Previous studies have reported equivocal findings regarding the effects of exercise on cardiac morphology and function. Guirado et al. [236] reported no changes in cardiac structure and diastolic function after 24 weeks of combined endurance and resistance training in individuals with high blood pressure. Pitsavos et al. [191] reported a reduction in resting heart rate, interventricular septum thickness, left ventricular posterior wall thickness, left ventricular end diastolic internal diameter, and left ventricular mass after 16 weeks of cycling training in high blood pressure adults. Turner et al. [229] reported a decrease in left ventricular posterior wall thickness and left ventricle mass index after 7 weeks of endurance training in older adults with high blood pressure. Hinderliter et al. [230] reported a reduction in interventricular septum thickness and left ventricular posterior wall thickness after 24 weeks of endurance training in overweight adults with high blood pressure. Rinder et al. [231] reported a reduction in interventricular septum thickness, left ventricular posterior wall thickness, and left ventricular mass after 24 weeks of endurance training in elderly individuals with high blood pressure. Lastly, Boman et al. [232] reported a reduction in heart rate, interventricular septum thickness, left ventricular posterior wall thickness, and left ventricular mass in a physically active individuals with high blood pressure compared to sedentary individuals with high blood pressure. Based on the findings of these previous studies, exercise may reverse pathological left ventricular remodeling in middle-age and elderly adults with high blood pressure. Potential mechanisms have been studied in animal models with high blood pressure, who have described that exercise reduces apoptosis in cardiomyocytes, increases vagal tone, and improves coronary circulation [228]. Additionally, in the present study, no clinically meaningful change was observed for systolic function following 6 weeks of boxing training in individuals with elevated blood pressure or stage 1 hypertension (Table 8). Although a significant lower ejection fraction

was detected in the control group (~55.2%) in comparison to the boxing group (~61.6%) at the end of the intervention, the difference in ejection fraction over time for both groups was less than 1%. Moreover, pre- and post- ejection fraction estimations in both groups were within normal limits (52-74%) [342].

5.2.6. Body Composition

Conflicting findings have been described regarding the effectiveness of exercise training to reduce weight and BMI and to have the ability to modify body composition independently [343-345]. In the present study, no changes in weight, BMI, %BF, lean mass, fat mass, fat free mass, bone mineral content, or bone mineral density were reported after 6 weeks of boxing training in individuals with elevated blood pressure or stage 1 hypertension (Table 9). Weight and BMI findings from the present study were in agreement with the findings from Beck et al. [215] who reported no weight or BMI changes after 8 weeks of endurance or resistance training in individuals with elevated blood pressure or stage 1 hypertension, and Schultz et al.[53] who also reported no weight or BMI changes after 12 weeks of boxing training in obese adolescent males. In contrast, Cheema et al. [52] reported reductions in weight and BMI by 4.1% and 4%, respectively, after 16 weeks of boxing training in adults with abdominal obesity. Interestingly, in the present study a weight gain of ~1 kg was observed at the end of the intervention in the control group. About 70% of this weight gain corresponded to fat mass. Young adults tend to increase their weights during college, which is closely associated to physical inactivity and poor eating habits [346]. Boxing training may confer some degree of protection against weight gains in young adults who attend college.

There is limited evidence overall on the effects of exercise training on body composition measured by DXA in high blood pressure population. For example, Tomeleri et al. [347] reported an increase in lean mass and a reduction in %BF after 12 weeks of resistance training in older women with high blood pressure. These findings were not consistent with those of the present study, which could be explained due to differences in sample size, age, and exercise program characteristics among studies, especially program length.

Finally, few studies have evaluated the effects of impact loading during exercise on bone structure. For example, Bassey et al. [348] reported an increase in bone mineral density at the trochanteric region of the femur after 24 weeks of intermittent lower-body high-impact exercise training in premenopausal women. Kato et el. [349] reported an increase in bone mineral density at the femoral neck after 24 weeks of low-repetition and high-impact training (e.g. 30 maximum jumps per week) in female college students. Vainionpaa et al. [350] reported an increase in bone mineral density at the femoral neck, trochanteric, and intertrochanteric regions after 48 weeks of lower-body high-impact exercises in premenopausal females. Lastly, Lambert et al. [351] reported an increase in areal bone mineral density at the radius after 40 weeks of high-impact training that included upper-body punches in young healthy women. These findings reflect a site-specific bone response to the mechanical load. The differences between these findings and those from the present study may be explained in large part due to the different duration of the training programs (e.g. 6 weeks versus minimum 24 weeks) and the use of different DXA settings during image acquisition (i.e. whole body vs. specific region).

5.2.7. Lipid Profile

Current clinical guidelines employ the lipid profile to estimate CVD risk [352,353]. Time course reductions in LDL-C, total cholesterol, and triglycerides and an increase in HDL-C have been shown to prevent CVD development [354]. In the present study, no changes in lipid profile were described after 6 weeks of boxing training in individuals with elevated blood pressure or stage 1 hypertension (Table 10). These findings were similar to Jarrete et al. [355] and Arca et al. [356] who also reported no lipid profile modifications after 8-week endurance training and 12-week aquatic training, respectively, in high blood pressure women. However, the findings of the present study were not in agreement with other studies. Ammar et al. [357] reported that 12 weeks of endurance training in women with high blood pressure reduced LDL-C and increased HDL-C. Zaros et al. [358] reported that 24 weeks of cycling training in women with high blood pressure reduced total cholesterol. Lastly, Tsai et al. [173] reported reductions in total cholesterol, LDL-C and triglycerides and an increase in HDL-C after 12 weeks of endurance training in individuals with high blood pressure. These equivocal findings may be explained due to the differences in exercise prescription among studies, or mainly, the duration of the exercise program. In general, studies that have shown LDL-C reductions with exercise training relate their effects to a concurrent weight loss rather than being produced by exercise itself. Meanwhile, an increase in HDL-C is directly related to exercise training [359].

5.2.8. Quality of Life

Previous reports have established lower quality of life in individuals with high blood pressure compared to normotensive individuals by using the SF-36 test [112-115]. Reversing

high blood pressure has not shown to substantially improve quality of life. This suggests that quality of life is more closely related to the presence of comorbidities [360].

In the present study, 6 weeks of boxing training significantly increased the perception of general health (Table 11). Previous studies evaluating the effects of exercise on quality of life in individuals with high blood pressure have reported equivocal results that could be explained by differences in sample size or broad inter-individual variability. For example, Cheema et al. [52] reported an improvement in physical functioning, vitality, and general health in adults with abdominal obesity and high blood pressure after 12-week of boxing training. Additionally, Molmen-Hansen et al. [192] reported an improvement in general health, social function, and physical function in individuals with high blood pressure after 12 weeks of HIIT. Finally, Tsai et al. [179] reported improvements in every domain except mental health in 52 Taiwanese individuals with high blood pressure after 10 weeks of endurance training. The improvement in general health due to exercise in the present study was the only domain that showed an agreement with previous studies. Presumably, the improvement in cardiorespiratory fitness positively affected the general health perception. In addition, our population was rather young (~25 years old) what could explain a higher baseline quality of life already. Interestingly, in the present study reductions in role limitations due physical health problems and role limitations due emotional problems were observed in the control group. These findings could be related to stress-related college factors such as poor sleep quality, academic performance, or economic burden [361].

5.3. Vascular Adaptations

Exercise-induced vascular adaptations have been extensively reported in healthy and CVD individuals, including those suffering from high blood pressure [21,239]. These adaptations are vessel-specific (e.g. elastic, conduit, and resistance arteries) [21] and are activity-dependent (e.g. upper body versus lower body exercise) [240,241].

The present study demonstrated that 6 weeks of boxing training improves conduit artery endothelial function in individuals with elevated blood pressure or stage 1 hypertension. Specifically, brachial and popliteal mean FMD% increased by 3% and 2.6%, respectively (Table 12, Figure 12, and Figure 13). These findings were in agreement with the findings of Tinken et al. [362] who reported that brachial and popliteal FMD% increased by 1.7% and 1.6% in normotensive individuals after 6 weeks of endurance training. Similarly, Beck et al. [215] showed an increase in brachial FMD% after 8 weeks of endurance training (~3.7%) and after 8 weeks of resistance training (~2.1%) in individuals with elevated blood pressure or stage 1 hypertension. In the same study, Beck et al. described a blunted endothelial response to hyperemia in individuals with elevated blood pressure or stage 1 hypertension compared to normotensive matched controls before the exercise intervention. The findings of the present study were also in agreement with previous studies involving individuals with high blood pressure. For example, Westhoff et al. [244] showed a 2.3% increase in brachial FMD% after 12-week endurance training in elderly hypertensive individuals. Swift et al. [245] reported an increase in brachial FMD% ranging from 1% to 1.5% after 24 weeks of endurance training in postmenopausal women with hypertension. Nualnim et al. [243] reported a ~3.9% increase in brachial FMD% after 12 weeks of swimming training in adults >50 years old with high blood pressure. Finally, Molmen-Hansen et al. [192] reported a 4.2% increase in brachial FMD% after

12 weeks of HIIT in individuals with high blood pressure. These FMD% improvements might be explained by an increase in ESS during exercise, which in turn increases NO and decreases inflammation [21,363-365]. Contrary to the present findings, no changes in brachial FMD% were reported by Westhoff et al. [185] in individuals with high blood pressure after 12-weeks of upper-body endurance exercise. Differences in endothelial responses in the present study and those of Westhoff et al. may be explained by a lower ESS stimulus produced during arm-cranking in comparison to whole body exercise. For its part, Spence et al. [141] reported a significant improvement in brachial FMD% after 24 weeks of resistance training (~1.9%) but not after 24 weeks of endurance training in young healthy individuals, while no changes were observed in femoral FMD% with either training modality.

In addition, the present study showed equivocal effects on the structure of conduit arteries after 6 weeks of boxing training in individuals with elevated blood pressure or stage 1 hypertension. Specifically, there were significant increases in resting artery diameter, in the common carotid artery (~0.3 mm) and in the popliteal artery (~0.2 mm) at the end of the intervention but not in the brachial artery (Table 12, Figure 12, Figure 13, and Figure 14). Similar findings have been described in previous studies. Dinenno et al. [366] reported an increase in diameter in the femoral artery (~0.8 mm) but not in the brachial artery after ~14 weeks of walking or jogging training in normotensive sedentary individuals. Spence et al. [141] reported an increase in diameter in the brachial artery (~0.3 mm) with resistance training but no change with endurance training, an increase in diameter in the femoral artery diameter (~0.2 mm) with endurance training but not with resistance training, and no change in diameter in the carotid artery following either exercise training modality in young healthy individuals. In contrast, no exercise-induced structural adaptations have been described in previous studies that

involved individuals with high blood pressure. For example, Nualnim et al. [243] reported no changes in brachial and carotid artery diameters after 12 weeks of swimming training in adults >50 years old with high blood pressure and Beck et al. [215] reported no change in brachial artery diameter after 8 weeks of endurance or resistance training in individuals with elevated blood pressure or stage 1 hypertension. Finally, the findings of the present study were not entirely consistent with those of Tinken et al. [362] who reported no changes in brachial and popliteal diameters in normotensive individuals throughout 8 weeks of endurance training. However, Tinken et al. described a progressive increment in vasodilator capacity in both brachial and popliteal arteries starting from week 2 in the same study, which can be interpreted as an expression of artery remodeling. It has been suggested that adaptations of conduit arteries to exercise training begin with an increase in endothelial function during the first weeks, followed by artery remodeling (e.g. increase in diameter) to normalize resting ESS [21,362]. The results from the present study support this last theory considering that resting ESS was not affected in the carotid and popliteal artery after the boxing intervention despite the increase in diameters in both arteries.

Further, resistance vessel adaptations were also observed in the present study through venous occlusion plethysmography. The present boxing protocol increased baseline forearm blood flow (~27%), peak forearm blood flow (~22%), and peak calf blood flow (~26%) (Table 12 and Figure 15). These changes reflected an augmented vascular ceiling capacity due to capillary or arteriolar proliferation and an improvement in endothelial function. These findings were in agreement with previous studies. Higashi et al. [167] reported an increase in peak forearm blood flow (~23%) in individuals with high blood pressure were observed after 12-weeks of brisk-walking, although baseline forearm blood flow remained unchanged after the

intervention. Beck et al. [246] reported an increase in baseline forearm blood flow (~22%), peak forearm flow (~31%), baseline calf blood flow (~33%), and peak calf blood flow (~44%) after 8 weeks of endurance or resistance training. Additionally, Beck et al. described that endothelial function of resistance vessels was impaired in individuals with elevated blood pressure or stage 1 hypertension compared to normotensive controls. Based on previous studies, the findings from the present study could be explained by a reduction in sympathetic tone, metabolic changes (e.g. Angiotensin II and Endothelin-1 downregulation), and an increase in ESS [21].

5.3.1. Nitric oxide bioavailability

NO is a key molecule in the maintenance of vascular homeostasis and vascular health. NO is produced by eNOS from its substrate, L-arginine, in endothelial cells. One of the most important functions of NO is to act as a vasodilator by relaxing smooth muscle cells from the tunica media of an artery. Also, NO can inhibit platelet adhesion and aggregation, decrease ROS formation, and reduce inflammation. All these functions prevent endothelial dysfunction, which is the first step in the development of CVD [367].

As NO half-life is relatively short, its direct quantification in blood is difficult. Estimations of NO production is best accomplished by quantification of the final NO metabolites nitrite/nitrate (NOx) [347]. The present study demonstrated that 6 weeks of boxing training in individuals with elevated blood pressure or stage 1 hypertension elevates NOx in plasma by nearly 27% (Table 13 and Figure 16). These results were in agreement with the findings of Beck et al. [215] who reported an increase in NOx after 8 weeks of cycling (~31%) and resistance training (~19%) in young individuals with elevated blood pressure or stage 1 hypertension. Similarly, Tomeleri et al. [347] reported an increase in NOx after 12 weeks of resistance training

(~35%) in older women with high blood pressure, while Izadi et al. [193] reported an increment in NOx after 6 weeks of HIIT (~140%) in elderly individuals with high blood pressure. Additionally, Hasegawa et al. [368] reported an increase in NOx after 6 weeks of HIIT (~31%) and after 8 weeks of moderate-intensity cycling (~43%) in healthy young men. Moreover, Maeda et al. [178] reported an increase in NOx (~60%) following 12 weeks of cycling at 80% of the ventilatory threshold in healthy elderly women.

The potential mechanisms by which exercise might increases NO bioavailability in plasma are not yet fully understood. However, it is believed that vascular homeostasis is closely regulated by the mechanical interaction between blood flow and the endothelium through a process known as ESS [369]. During exercise, there is a raise on pulsatility and ESS inside arteries [21,370], which suggests that these hemodynamic changes may regulate the expression of genes involved in NO production through a mechanotransduction pathway [21,62,371].

5.3.2. Inflammation

Low-grade chronic inflammation has been described as a hallmark in the physiopathology of high blood pressure [83,372,373]. TNF-α, IL-6, and CRP are classic inflammatory biomarkers employed to explore the inflammatory state of an individual [86,90,374]. Several studies have shown a direct correlation between these biomarkers and high blood pressure [86,89,375,376]. TNF-α is a primary inflammatory cytokine released by white blood cells that stimulate visceral adipose tissue to secrete IL-6, a secondary inflammatory cytokine, which in turn increases the production and excretion of CRP from the hepatocyte [376-378]. Additionally, CRP can be secreted by other cell types including endothelial cells [379], where it has shown to have deleterious autocrine and paracrine effects on them (e.g.

overexpression of adhesion molecules) [380-382]. In the present study, CRP but neither TNF-α or IL-6 decreases after 6 weeks of boxing training (Table 13 and Figure 17). These findings can be explained due the fact that a short period of exercise training (e.g. 6 weeks) by itself does not significantly affect body fat mass and specifically the amount of adipose tissue, consequently, there may be no major modification in the adipocyte signaling pathway to alter TNF-α and IL-6 production. Conversely, CRP reductions could be the result of an exercise-induced signal (e.g. mechanotransduction or myokines) that directly enhance endothelial function and inhibit CRP secretion to the blood stream. A reduction of CRP might express a direct downregulation of vascular inflammation that helps prevent high blood pressure.

The results of the present study were in agreement with those of Lamina et al. [249] who reported a CRP reduction after 8 weeks of cycling training at moderate intensity in individuals with high blood pressure. Interestingly, baseline CRP levels differed between studies. While Lamina et al. study reported a baseline mean CRP value below 1 mg/L, which is considered to be in the non-inflammatory range, the present study showed a baseline mean CRP was above 3 mg/L (Table 13), which is categorized as high risk for the development of cardiovascular events [382,383]. These results confirm that exercise can be employed as an anti-inflammatory strategy for individuals with high blood pressure.

5.3.3. Oxidative Stress

Oxidative stress is another feature associated with the pathophysiology of high blood pressure [8,82,83]. In the present study, no changes were observed in oxidative stress status as observed by the measurements of 8-isoprostane, SOD, and TAC in the plasma of individuals with elevated blood pressure or stage 1 hypertension after 6 weeks of boxing training (Table 13).

These findings were incongruent with previous studies. Feairheller et al. [252] reported an increase in plasma TAC (~9%) and urinary 8-isoprostane (~31%) after 24 weeks of endurance training at 70%VO_2max in individuals with high blood pressure. Beck et al. [246] reported a reduction in plasma 8-isoprostane (~43%) and an increase in plasma TAC (~43%) after 8 weeks of resistance training and a reduction in plasma 8-isoprostane (~40%) and an increase in plasma TAC (~42%) after 8 weeks of endurance training in individuals with elevated blood pressure and stage 1 hypertension. Lastly, Dantas et al. [253] reported an increase in plasma TAC (~12%) after 12 weeks of resistance training in elderly women with high blood pressure. Differences in the oxidative stress responses between the present study and previous studies may be explained by the length of each exercise program. The present study involved only 6 weeks of training while the other studies lasted from 8 to 24 weeks.

5.4. Blood Flow Characterization

Physically active individuals have a reduced cardiovascular risk compared to those that are physically inactive. More than 50% of the cardiovascular benefits of physical activity are not yet explained by the reduction of classic CVD risk factors (e.g. high blood pressure, obesity, and dyslipidemia), meaning that other underlying physiological mechanisms may be involved in the prevention of CVD [21]. One such physiological mechanism thought to contribute to the prevention of CVD is the mechanical effect of pulsatile blood flow on the vascular wall during exercise [23,384]. Exercise-induced blood flow regulates vascular homeostasis through cellular mechanotransduction pathways [62]. Importantly, this regulation is vessel-specific and is dependent on blood flow characteristics [21,63,64].

The present study is the first one to characterize blood flow in the common carotid artery according to its directionality, ESS magnitude, and blood flow pattern during boxing training in individuals with elevated blood pressure or stage 1 hypertension. Additionally, to the best of our knowledge, the present study is the first one to analyze blood flow in the carotid artery during an exercise modality different to cycling or walking [384-389]. In the present study, we demonstrated that blood flow characteristics in the common carotid artery change from resting to boxing training conditions. First, both anterograde and retrograde ESS magnitudes increased in an intensity-dependent manner during exercise. Second, blood flow directionality changed from solely anterograde at rest to anterograde and retrograde during exercise (Figure 18). Third, turbulent blood flow was the only pattern observed for anterograde blood flow during exercise, while laminar blood flow and a transition from laminar to turbulent blood flow were observed at 60% and 95% VO_2max for retrograde blood flow, respectively (Figure 19).

Findings described within the present study are similar to those of Liu et al. [384] and modeled by Wang et al. [390] who reported an increase from baseline in both anterograde and retrograde ESS in the right common carotid artery during cycling in healthy individuals. Additionally, Wang et al. reported that ESS increased in an intensity-manner. Similarly, Coovert et al. [391] reported an increase in anterograde and retrograde shear rate, an ESS surrogate, in the brachial artery during cycling that were dependent on the intensity of the activity in healthy individuals. Several *in vitro* studies, simulating exercise conditions, have shown beneficial adaptations in endothelial cells exposed to incremental ESS (e.g. eNOS upregulation) [34,271,273,392]. However, a recent *in vitro* experiment showed that moderate-intensity ESS induced higher intracellular NO levels compared to high-intensity ESS [390]. These findings suggest that vascular adaptations may vary according to the exercise dose.

In the present study, turbulent blood flow was the predominant blood flow pattern observed during boxing training at both 60% and 95%VO_2max (Figure 19). Similar to the findings of the present study, Gurovich & Braith [68] reported the presence of anterograde turbulent blood flow in the brachial and femoral arteries during cycling and resistance training in healthy individuals when the intensity was at 40% or above their maximal exercise capacity for each type of activity. Additionally, they also reported a transition from laminar to turbulent retrograde blood flow in the brachial and femoral arteries when the exercise intensity was at 40% or above, except for the femoral artery during resistance training where a laminar retrograde pattern was observed. Moreover, we recently reported the association of hyperemic turbulent blood flow to peak brachial artery dilation during FMD, which is an endothelium-dependent test [369]. These findings suggest that turbulent blood flow may be also favorable to maintain vascular homeostasis.

Altogether, the present study confirms that ESS increased during boxing training which may partially explain the improvements in cardiovascular health observed in individuals with elevated blood pressure or stage 1 hypertension after 6 weeks of boxing training.

5.5. Limitations and Future Research

The present study was not without limitations. First, only young adults (<35 years old) participated in this study, which may limit the generalization of the present results to only young individuals with elevated blood pressure or stage 1 hypertension. Second, a dietary record was not employed to ensure that a low-nitrate diet was followed prior blood collection, which could have affected the results of some biomarkers. Third, some feasibility outcomes regarding the boxing training intervention were not explored in the present study such as enjoyment, exercise

tolerance, feelings, and intention to participate [393], which could have been valuable information for the planning of future studies that would involve this type of training. Fourth, the DXA scan did not include specific sites (e.g. distal radius) to measure bone changes following the intervention, which could have reduced the accuracy to detect bone remodeling due to boxing training. Lastly, structural adaptations in muscular arteries may be better represented by the conduit dilator capacity rather than the artery diameter, which was not measured in the present study.

Future boxing training studies in individuals with elevated blood pressure or stage 1 hypertension should include an elderly population or be part of a community-based program to determine if the results of the present study can be generalized. Finally, the *in vivo* blood flow characteristics obtained acutely during boxing training may be employed in future *in vitro* studies with human carotid endothelial cells to determine the best training protocol to upregulate or downregulate genes involved with vascular homeostasis.

5.6. Conclusions

In conclusion, the present study demonstrated that a 6-week, 3 days per week, polarized boxing training program successfully reduced SBP, DBP, cSBP, and resting heart rate, while improving cardiorespiratory fitness, vascular health, and quality of life in individuals with elevated blood pressure or stage 1 hypertension. These effects may be explained, in part, to an increase in ESS during exercise, which can reverse some pathological pathways involved with high blood pressure such as endothelial dysfunction, NO bioavailability, peripheral vascular resistance, and inflammation. Further, boxing training could be recommended as a nontraditional exercise alternative in the management of high blood pressure.

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APPENDIX A

Boxing Training Program

Week 1

Day 1 (/ /)

1) 50% → ____ bpm

1, 1, 2, 1, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

2) 95% → ____ bpm

1, 2, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

3) 95% → ____ bpm

3, 4, 3, 4, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

4) 95% → ____ bpm

5, 6, 5, 6, 5, 6 (Mitt)

Min	1	2	3
HR			

5) 50% → ____ bpm

3-b, 4-b, 3, 4, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

6) 50% → ____ bpm

1, 2, 3, 4, 3-b, 4-b (Mitt)

Min	1	2	3
HR			

7) 50% → ____ bpm

3-b, 4-b, 3-b, 4-b, 1, 2 (Mitt)

Min	1	2	3
HR			

8) 50% → ____ bpm

3-b, 3, 4-b, 4, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

9) 50% → ____ bpm

1, 2, 1, 2, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

10) 50% → ____ bpm

1-b, 2-b, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

1=Jab, 2=Straight, 3=Left hook, 4=Right Hook, 5=Left Uppercut, 6=Right Uppercut. b=body

Rounds = 3 min; Rest = 1 min

Day 2 (/ /)

1) 50% → ____ bpm

1, 2, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

2) 95% → ____ bpm

1, 2, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

3) 95% → ____ bpm

3, 4, 3, 4, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

4) 95% → ____ bpm

5, 6, 5, 6, 5, 6 (Mitt)

Min	1	2	3
HR			

5) 50% → ____ bpm

1, 2, 3, 4, 1, 2. Step (Heavy Bag)

Min	1	2	3
HR			

6) 50% → ____ bpm

1, 2, 3, 4, 5, 6 (Mitt)

Min	1	2	3
HR			

7) 50% → ____ bpm

3-b, 4-b, 3-b, 4-b, 5, 6 (Mitt)

Min	1	2	3
HR			

8) 50% → ____ bpm

3-b, 3, 4-b, 4, 1, 2. Step (Heavy Bag)

Min	1	2	3
HR			

9) 50% → ____ bpm

1, 2, 1, 2, 1, 2. Duck (Heavy Bag)

Min	1	2	3
HR			

1-b, 2-b, 1, 2, 1-b, 2-b (Heavy Bag)

Min	1	2	3
HR			

1=Jab, 2=Straight, 3=Left hook, 4=Right Hook, 5=Left Uppercut, 6=Right Uppercut. b=body

Rounds = 3 min; Rest = 1 min

Day 3 (/ /)

1) 50% → ____ bpm

3-b, 4-b, 3-b, 4-b, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

2) 95% → ____ bpm

1, 2, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

3) 95% → ____ bpm

3-b, 4-b, 3-b, 4-b, 3-b, 4-b (Heavy Bag)

Min	1	2	3
HR			

4) 95% → ____ bpm

5, 6, 5, 6, 5, 6 (Mitt)

Min	1	2	3
HR			

5) 50% → ____ bpm

3-b, 3, 4-b, 4, 1, 2. Step (Heavy Bag)

Min	1	2	3
HR			

6) 50% → ____ bpm

1, 2, Duck, Duck, 3-b, 4-b (Mitt)

Min	1	2	3
HR			

7) 50% → ____ bpm

3-b, 4-b, 3-b, 4-b, 1, 2 (Mitt)

Min	1	2	3
HR			

8) 50% → ____ bpm

3-b, 3, 4-b, 4, 1, 2. Step (Heavy Bag)

Min	1	2	3
HR			

9) 50% → ____ bpm

1, 1, 2, 1, 1, 2. Step (Heavy Bag)

Min	1	2	3
HR			

10) 50% → ____ bpm

5, 6, 5, 6, 5, 6. Step (Heavy Bag)

Min	1	2	3
HR			

1=Jab, 2=Straight, 3=Left hook, 4=Right Hook, 5=Left Uppercut, 6=Right Uppercut. b=body

Rounds = 3 min; Rest = 1 min

Week 2

Day 1 (/ /)

1) 50% → ____ bpm

1, 2, 3, 4, 3-b, 4-b (Heavy Bag)

Min	1	2	3
HR			

2) 95% → ____ bpm

1, 2, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

3) 95% → ____ bpm

3, 4, 3, 4, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

4) 95% → ____ bpm

5, 6, 5, 6, 5, 6 (Mitt)

Min	1	2	3
HR			

5) 50% → ____ bpm

3-b, 4-b, 3, 4, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

6) 50% → ____ bpm

1, 2, 3, 4, 3-b, 4-b. Step (Mitt)

Min	1	2	3
HR			

7) 50% → ____ bpm

3-b, 4-b, Duck, Duck, 1, 2 (Mitt)

Min	1	2	3
HR			

8) 50% → ____ bpm

3-b, 3, 4-b, 4, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

9) 50% → ____ bpm

1, 2, 1, 2, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

10) 50% → ____ bpm

1-b, 2-b, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

1=Jab, 2=Straight, 3=Left hook, 4=Right Hook, 5=Left Uppercut, 6=Right Uppercut. b=body

Rounds = 3 min; Rest = 1 min

Day 2 (/ /)

1) 50% → ____ bpm

3-b, 3, 4-b, 4, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

2) 95% → ____ bpm

1, 2, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

3) 95% → ____ bpm

3, 4, 3, 4, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

4) 95% → ____ bpm

5, 6, 5, 6, 5, 6 (Mitt)

Min	1	2	3
HR			

5) 50% → ____ bpm

1, 2, 3, 4, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

6) 50% → ____ bpm

1, 2, 3, 4, 3-b, 4-b (Mitt)

Min	1	2	3
HR			

7) 50% → ____ bpm

3-b, 4-b, 3-b, 4-b, 3-b, 4-b. (Mitt)

Min	1	2	3
HR			

8) 50% → ____ bpm

3-b, 3, 4-b, 4, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

9) 50% → ____ bpm

1, 2, 1, 2, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

10) 50% → ____ bpm

1-b, 2-b, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

1=Jab, 2=Straight, 3=Left hook, 4=Right Hook, 5=Left Uppercut, 6=Right Uppercut. b=body

Rounds = 3 min; Rest = 1 min

Day 3 (/ /)

1) 50% → ____ bpm

1, 1, 2, 1, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

2) 95% → ____ bpm

1, 2, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

3) 95% → ____ bpm

3, 4, 3, 4, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

4) 95% → ____ bpm

5, 6, 5, 6, 5, 6 (Mitt)

Min	1	2	3
HR			

5) 50% → ____ bpm

3-b, 4-b, 3, 4, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

6) 50% → ____ bpm

1, 2, 3, 4, 3-b, 4-b (Mitt)

Min	1	2	3
HR			

7) 50% → ____ bpm

3-b, 4-b, 3-b, 4-b, 1, 2 (Mitt)

Min	1	2	3
HR			

8) 50% → ____ bpm

3-b, 3, 4-b, 4, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

9) 50% → ____ bpm

1, 2, 1, 2, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

10) 50% → ____ bpm

1-b, 2-b, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

1=Jab, 2=Straight, 3=Left hook, 4=Right Hook, 5=Left Uppercut, 6=Right Uppercut. b=body

Rounds = 3 min; Rest = 1 min

Week 3

Day 1 (/ /)

1) 50% → ____ bpm

1, 2, 2, 1, 2, 2 (Heavy Bag)

Min	1	2	3
HR			

2) 95% → ____ bpm

1, 2, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

3) 95% → ____ bpm

3, 4, 3, 4, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

4) 95% → ____ bpm

5, 6, 5, 6, 5, 6 (Mitt)

Min	1	2	3
HR			

5) 50% → ____ bpm

1-b, 2-b, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

6) 50% → ____ bpm

1, 2, 3, 4, 3-b, 4-b (Mitt)

Min	1	2	3
HR			

7) 50% → ____ bpm

3-b, 4-b, 3-b, 4-b, 1, 2 (Mitt)

Min	1	2	3
HR			

8) 50% → ____ bpm

3-b, 3, 4-b, 4, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

9) 50% → ____ bpm

1, 2, 1, 2, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

10) 50% → ____ bpm

3-b, 4-b, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

1=Jab, 2=Straight, 3=Left hook, 4=Right Hook, 5=Left Uppercut, 6=Right Uppercut. b=body

Rounds = 3 min; Rest = 1 min

Day 2 (/ /)

1) 50% → ____ bpm

3-b, 4-b, 3, 4, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

2) 95% → ____ bpm

1, 2, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

3) 95% → ____ bpm

3, 4, 3, 4, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

4) 95% → ____ bpm

5, 6, 5, 6, 5, 6 (Mitt)

Min	1	2	3
HR			

5) 50% → ____ bpm

3-b, 4-b, 3, 4, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

6) 50% → ____ bpm

1, 2, 5, 6, 5, 6 (Mitt)

Min	1	2	3
HR			

7) 50% → ____ bpm

3-b, 4-b, 3-b, 4-b, 1, 2 (Mitt)

Min	1	2	3
HR			

8) 50% → ____ bpm

3-b, 3, 4-b, 4, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

9) 50% → ____ bpm

1, 2, 1, 2, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

10) 50% → ____ bpm

1-b, 2-b, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

1=Jab, 2=Straight, 3=Left hook, 4=Right Hook, 5=Left Uppercut, 6=Right Uppercut. b=body

Rounds = 3 min; Rest = 1 min

Day 3 (/ /)

1) 50% → ____ bpm

1, 1, 2, 1, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

2) 95% → ____ bpm

1, 2, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

3) 95% → ____ bpm

3, 4, 3, 4, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

4) 95% → ____ bpm

5, 6, 5, 6, 5, 6 (Mitt)

Min	1	2	3
HR			

5) 50% → ____ bpm

3-b, 4-b, 3, 4, 1, 2. Step (Heavy Bag)

Min	1	2	3
HR			

6) 50% → ____ bpm

1, 2, 3, 4, 3-b, 4-b (Mitt)

Min	1	2	3
HR			

7) 50% → ____ bpm

3-b, 4-b, Duck, Duck, 1, 2 (Mitt)

Min	1	2	3
HR			

8) 50% → ____ bpm

3-b, 3, 4-b, 4, 1, 2. Step (Heavy Bag)

Min	1	2	3
HR			

9) 50% → ____ bpm

1, 2, 1, 2, 3, 4. Step (Heavy Bag)

Min	1	2	3
HR			

10) 50% → ____ bpm

1-b, 2-b, 1, 2, 1, 2. Step (Heavy Bag)

Min	1	2	3
HR			

1=Jab, 2=Straight, 3=Left hook, 4=Right Hook, 5=Left Uppercut, 6=Right Uppercut. b=body

Rounds = 3 min; Rest = 1 min

Week 4

Day 1 (/ /)

1) 50% → ____ bpm

1, 1, 2, 1, 1, 2. Step (Heavy Bag)

Min	1	2	3
HR			

2) 95% → ____ bpm

1, 2, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

3) 95% → ____ bpm

3, 4, 3, 4, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

4) 95% → ____ bpm

5, 6, 5, 6, 5, 6 (Mitt

Min	1	2	3
HR			

5) 50% → ____ bpm

3-b, 4-b, 3, 4, 1, 2. Step (Heavy Bag)

Min	1	2	3
HR			

6) 50% → ____ bpm

1, 2, 5, 6, 3-b, 4-b (Mitt)

Min	1	2	3
HR			

7) 50% → ____ bpm

1, 2, 5, 6, 3-b, 4-b (Mitt)

Min	1	2	3
HR			

8) 50% → ____ bpm

3-b, 3, 4-b, 4, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

9) 50% → ____ bpm

1, 2, 1, 2, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

10) 50% → ____ bpm

1-b, 2-b, 1, 2, 1, 2. Step (Heavy Bag)

Min	1	2	3
HR			

1=Jab, 2=Straight, 3=Left hook, 4=Right Hook, 5=Left Uppercut, 6=Right Uppercut. b=body

Rounds = 3 min; Rest = 1 min

Day 2 (/ /)

1) 50% → ____ bpm

1, 2, 3, 4, 1, 2. Step (Heavy Bag)

Min	1	2	3
HR			

2) 95% → ____ bpm

1, 2, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

3) 95% → ____ bpm

3, 4, 3, 4, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

4) 95% → ____ bpm

5, 6, 5, 6, 5, 6 (Mitt)

Min	1	2	3
HR			

5) 50% → ____ bpm

3-b, 4-b, 1, 2, 3, 4. Step (Heavy Bag)

Min	1	2	3
HR			

6) 50% → ____ bpm

5, 6, 5, 6, 3-b, 4-b (Mitt)

Min	1	2	3
HR			

7) 50% → ____ bpm

3-b, 4-b, 1, 2, 3, 4 (Mitt)

Min	1	2	3
HR			

8) 50% → ____ bpm

3-b, 3, 4-b, 4, 1, 2. Step (Heavy Bag)

Min	1	2	3
HR			

9) 50% → ____ bpm

1, 2, 1, 2, 3, 4. Step (Heavy Bag)

Min	1	2	3
HR			

10) 50% → ____ bpm

1-b, 2-b, 1, 2, 1, 2. Step (Heavy Bag)

Min	1	2	3
HR			

1=Jab, 2=Straight, 3=Left hook, 4=Right Hook, 5=Left Uppercut, 6=Right Uppercut. b=body

Rounds = 3 min; Rest = 1 min

Day 3 (/ /)

1) 50% → ____ bpm

1, 1, 2, 1, 1, 2. Step (Heavy Bag)

Min	1	2	3
HR			

2) 95% → ____ bpm

1, 2, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

3) 95% → ____ bpm

3, 4, 3, 4, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

4) 95% → ____ bpm

5, 6, 5, 6, 5, 6 (Mitt)

Min	1	2	3
HR			

5) 50% → ____ bpm

3-b, 4-b, 3, 4, 1, 2. Step (Heavy Bag)

Min	1	2	3
HR			

6) 50% → ____ bpm

1, 2, 3, 4, 3-b, 4-b (Mitt)

Min	1	2	3
HR			

7) 50% → ____ bpm

3-b, 4-b, 3-b, 4-b, 1, 2 (Mitt)

Min	1	2	3
HR			

8) 50% → ____ bpm

3-b, 3, 4-b, 4, 1, 2. Step (Heavy Bag)

Min	1	2	3
HR			

9) 50% → ____ bpm

1, 2, 1, 2, 3, 4. Step (Heavy Bag)

Min	1	2	3
HR			

10) 50% → ____ bpm

1-b, 2-b, 1, 2, 1, 2. Step (Heavy Bag)

Min	1	2	3
HR			

1=Jab, 2=Straight, 3=Left hook, 4=Right Hook, 5=Left Uppercut, 6=Right Uppercut. b=body

Rounds = 3 min; Rest = 1 min

Week 5

Day 1 (/ /)

1) 50% → ____ bpm

1, 1, 2, 1, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

2) 95% → ____ bpm

1, 2, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

3) 95% → ____ bpm

3, 4, 3, 4, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

4) 95% → ____ bpm

5, 6, 5, 6, 5, 6 (Mitt)

Min	1	2	3
HR			

5) 50% → ____ bpm

3-b, 4-b, 3, 4, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

6) 50% → ____ bpm

1, 2, 3, 4, 3-b, 4-b (Mitt)

Min	1	2	3
HR			

7) 50% → ____ bpm

3-b, 4-b, 3-b, 4-b, 1, 2 (Mitt)

Min	1	2	3
HR			

8) 50% → ____ bpm

3-b, 3, 4-b, 4, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

9) 50% → ____ bpm

1, 2, 1, 2, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

10) 50% → ____ bpm

1-b, 2-b, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

1=Jab, 2=Straight, 3=Left hook, 4=Right Hook, 5=Left Uppercut, 6=Right Uppercut. b=body

Rounds = 3 min; Rest = 1 min

Day 2 (/ /)

1) 50% → ____ bpm

1, 1, 2, 1, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

2) 95% → ____ bpm

1, 2, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

3) 95% → ____ bpm

3, 4, 3, 4, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

4) 95% → ____ bpm

5, 6, 5, 6, 5, 6 (Mitt)

Min	1	2	3
HR			

5) 50% → ____ bpm

3-b, 4-b, 3, 4, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

6) 50% → ____ bpm

1, 2, 3, 4, 3-b, 4-b (Mitt)

Min	1	2	3
HR			

7) 50% → ____ bpm

3-b, 4-b, 3-b, 4-b, 1, 2 (Mitt)

Min	1	2	3
HR			

8) 50% → ____ bpm

3-b, 3, 4-b, 4, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

9) 50% → ____ bpm

1, 2, 1, 2, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

10) 50% → ____ bpm

1-b, 2-b, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

1=Jab, 2=Straight, 3=Left hook, 4=Right Hook, 5=Left Uppercut, 6=Right Uppercut. b=body

Rounds = 3 min; Rest = 1 min

Day 3 (/ /)

1) 50% → ____ bpm

1, 1, 2, 1, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

2) 95% → ____ bpm

1, 2, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

3) 95% → ____ bpm

3, 4, 3, 4, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

4) 95% → ____ bpm

5, 6, 5, 6, 5, 6 (Mitt)

Min	1	2	3
HR			

5) 50% → ____ bpm

3-b, 4-b, 3, 4, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

6) 50% → ____ bpm

1, 2, 3, 4, 3-b, 4-b (Mitt)

Min	1	2	3
HR			

7) 50% → ____ bpm

3-b, 4-b, 3-b, 4-b, 1, 2 (Mitt)

Min	1	2	3
HR			

8) 50% → ____ bpm

3-b, 3, 4-b, 4, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

9) 50% → ____ bpm

1, 2, 1, 2, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

10) 50% → ____ bpm

1-b, 2-b, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

1=Jab, 2=Straight, 3=Left hook, 4=Right Hook, 5=Left Uppercut, 6=Right Uppercut. b=body

Rounds = 3 min; Rest = 1 min

Week 6

Day 1 (/ /)

1) 50% → ____ bpm

1, 1, 2, 1, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

2) 95% → ____ bpm

1, 2, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

3) 95% → ____ bpm

3, 4, 3, 4, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

4) 95% → ____ bpm

5, 6, 5, 6, 5, 6 (Mitt)

Min	1	2	3
HR			

5) 50% → ____ bpm

3-b, 4-b, 3, 4, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

6) 50% → ____ bpm

1, 2, 3, 4, 3-b, 4-b (Mitt)

Min	1	2	3
HR			

7) 50% → ____ bpm

3-b, 4-b, 3-b, 4-b, 1, 2 (Mitt)

Min	1	2	3
HR			

8) 50% → ____ bpm

3-b, 3, 4-b, 4, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

9) 50% → ____ bpm

1, 2, 1, 2, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

10) 50% → ____ bpm

1-b, 2-b, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

1=Jab, 2=Straight, 3=Left hook, 4=Right Hook, 5=Left Uppercut, 6=Right Uppercut. b=body

Rounds = 3 min; Rest = 1 min

Day 2 (/ /)

1) 50% → ____ bpm

1, 1, 2, 1, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

2) 95% → ____ bpm

1, 2, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

3) 95% → ____ bpm

3, 4, 3, 4, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

4) 95% → ____ bpm

5, 6, 5, 6, 5, 6 (Mitt)

Min	1	2	3
HR			

5) 50% → ____ bpm

3-b, 4-b, 3, 4, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

6) 50% → ____ bpm

1, 2, 3, 4, 3-b, 4-b (Mitt)

Min	1	2	3
HR			

7) 50% → ____ bpm

3-b, 4-b, 3-b, 4-b, 1, 2 (Mitt)

Min	1	2	3
HR			

8) 50% → ____ bpm

3-b, 3, 4-b, 4, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

9) 50% → ____ bpm

1, 2, 1, 2, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

10) 50% → ____ bpm

1-b, 2-b, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

1=Jab, 2=Straight, 3=Left hook, 4=Right Hook, 5=Left Uppercut, 6=Right Uppercut. b=body

Rounds = 3 min; Rest = 1 min

Day 3 (/ /)

1) 50% → ____ bpm

1, 1, 2, 1, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

2) 95% → ____ bpm

1, 2, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

3) 95% → ____ bpm

3, 4, 3, 4, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

4) 95% → ____ bpm

5, 6, 5, 6, 5, 6 (Mitt)

Min	1	2	3
HR			

5) 50% → ____ bpm

3-b, 4-b, 3, 4, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

6) 50% → ____ bpm

1, 2, 3, 4, 3-b, 4-b (Mitt)

Min	1	2	3
HR			

7) 50% → ____ bpm

3-b, 4-b, 3-b, 4-b, 1, 2 (Mitt)

Min	1	2	3
HR			

8) 50% → ____ bpm

3-b, 3, 4-b, 4, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

9) 50% → ____ bpm

1, 2, 1, 2, 3, 4 (Heavy Bag)

Min	1	2	3
HR			

10) 50% → ____ bpm

1-b, 2-b, 1, 2, 1, 2 (Heavy Bag)

Min	1	2	3
HR			

1=Jab, 2=Straight, 3=Left hook, 4=Right Hook, 5=Left Uppercut, 6=Right Uppercut. b=body

Rounds = 3 min; Rest = 1 min

APPENDIX B

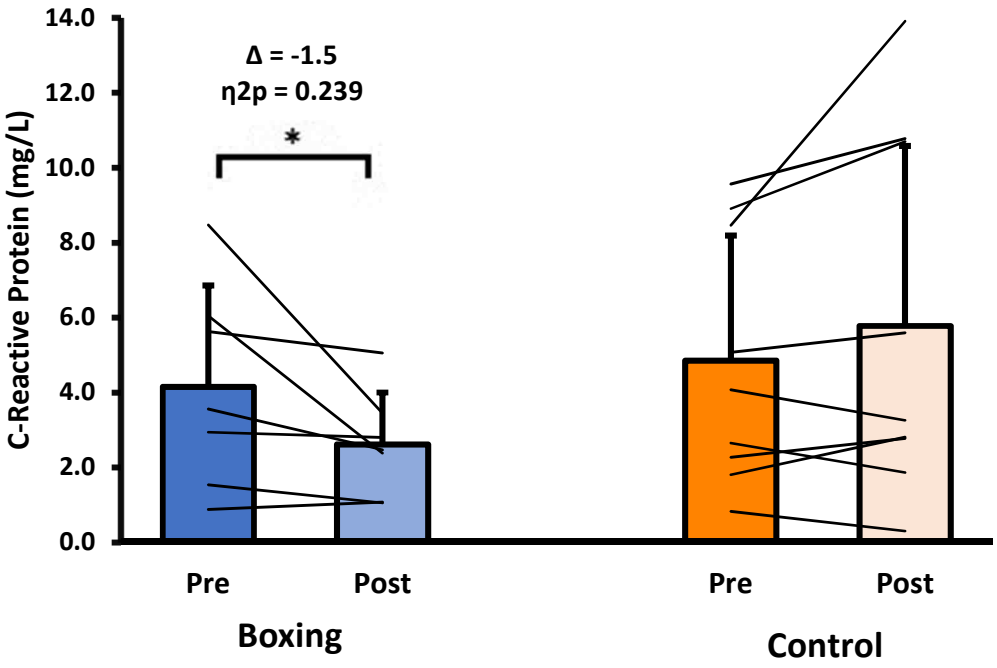

Figure 22. CRP changes following 6 weeks of boxing training in individuals with elevated blood pressure or stage 1 hypertension. * $p < 0.05$.

CURRICULUM VITA

Francisco Morales-Acuna was born in Santiago, Chile. He completed his Doctor of Medicine degree in 2009 at Universidad Andrés Bello, Chile. From 2010 to 2013, Francisco pursued a degree Master of Sciences in Sports Medicine at Universidad Mayor, Chile and at the same time he worked as a physician in an emergency room.

Next, he moved to Mexico to obtain his Sports Medicine Specialist degree at Universidad Autónoma del Estado de México. Then, he moved to Spain to complete a Fellowship in Sports Cardiology at the Sports Medicine Center of the Spanish Agency for Health Protection in Sport.

Finally, he began his doctoral studies as a Graduate Research Assistant in Dr. Alvaro Gurovich's Clinical Applied Physiology Lab in the Department of Physical Therapy, first at Indiana State University and then at The University of Texas at El Paso. As a doctoral student, Francisco was an instructor in the physician assistant cardiopulmonary course at Indiana State University. In addition, Francisco has published as a first author in European Journal of Applied Physiology, Clinical Physiology & Functional Imaging, and Revista Archivos de la Sociedad Chilena de Medicina del Deporte and as a co-author in Circulation: Cardiovascular Imaging, European Heart Journal Cardiovascular Imaging, Clinical Hypertension, and International Journal of Food Sciences and Nutrition. Francisco was also a co-author in the book chapter "Arrhythmias in the Athlete" of the Spaniard Cardiology Society.