EFFECTS OF EXERCISE THERAPY ON ARTERIAL STIFFNESS AND OTHER CARDIOVASCULAR RISK FACTORS IN PATIENTS WITH CARDIOMETABOLIC SYNDROME

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ABSTRACT

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Background: Exercise improves vascular function and hemodynamics. To demonstrate this, several studies have shown acute positive effects on arterial stiffness, blood pressure, and other cardiometabolic risk factors that are associated with overall cardiovascular health. However, longitudinal studies have yet to illustrate this hypothesis in exercise prescription research. The aim of this study is to exemplify the use of exercise therapy (ExT) to improve cardiovascular health risk factors in hospital outpatients with cardiometabolic syndrome.

Methods: This is a longitudinal cohort study to analyze vascular function, blood pressure, and lipid profile in adult hospital outpatients of Hospital Nova. The study follows up measured parameters of subjects after six-month exercise therapy. Arterial stiffness, blood pressure, body composition, lipid profile, and maximal oxygen uptake were evaluated prior to and after six months of exercise. Paired T-test was used to show changes between pre- and post-intervention.

Results: Eleven (11) subjects completed arteriograph measurements. There was a significant improvement in arterial stiffness after six months of exercise therapy [Δ=0.790 m/s, SD=0.802, t(10)=3.23, p=0.009]. Systolic and diastolic blood pressure also improved, however they are not statistically significant (SBP Δ: -2.27 mmHg, SD=10.1, t(10)=3.232, p=0.448; DBP Δ=-1.36 mmHg, SD=6.65, t(10)=3.232, p=0.476]. Similarly, blood cholesterol (Δ=-0.04, SD=0.360, p=0.681), high-density lipoprotein (Δ=+0.03, SD=0.360, p=0.583), low-density lipoprotein (Δ=-0.08, SD=0.256, p=0.273), triglycerides (Δ=0.12, SD=0.304, p=0.266), all improved but statistically insignificant and only high-sensitive c- reactive protein (Δ=1.32, SD=2.36, p=0.05) significantly improved. Maximal oxygen consumption has also deteriorated (Δ=+1.35, SD=3.77, p=0.264). In contrast, there were significant changes in body fat percentage (Δ=-2.59 %, SD=2.27, p<0.05), fat mass (Δ=-3.11kg, SD=4.39, p<0.05), visceral fat range (Δ=-27.94m^2, SD=23.39, p<0.05), and skeletal muscle mass (Δ=+1.14kg, SD=1.63, p<0.05)

Conclusions: Arterial stiffness and body composition improved after a six month exercise therapy in outpatients with cardiometabolic syndrome. These changes were independent from the changes seen in blood pressure and lipid profile.

Key words: arterial stiffness, exercise therapy, cardiometabolic syndrome

ABBREVIATIONS

aoPWV	aortic pulse wave velocity
baPWV	brachial-ankle pulse wave velocity
BP	blood pressure
cfPWV	carotid-femoral pulse wave velocity
CVD	cardiovascular disease
DBP	diastolic blood pressure
ExT	exercise therapy
MAP	mean arterial pressure
PWV	pulse wave velocity
SBP	systolic blood pressure
VEGF	vascular endothelial growth factor
VSMC	vascular smooth muscle cells

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1 INTRODUCTION

A major component of the cardiovascular system is the blood vessels. Composed of arteries, veins, and capillaries, these conduits are responsible for the distribution of oxygen, nutrients, and other substances to the organs and tissues. Figure 1 provides a schematic view of the cardiovascular system and its major components: heart, central and peripheral blood vessels, and the lungs.

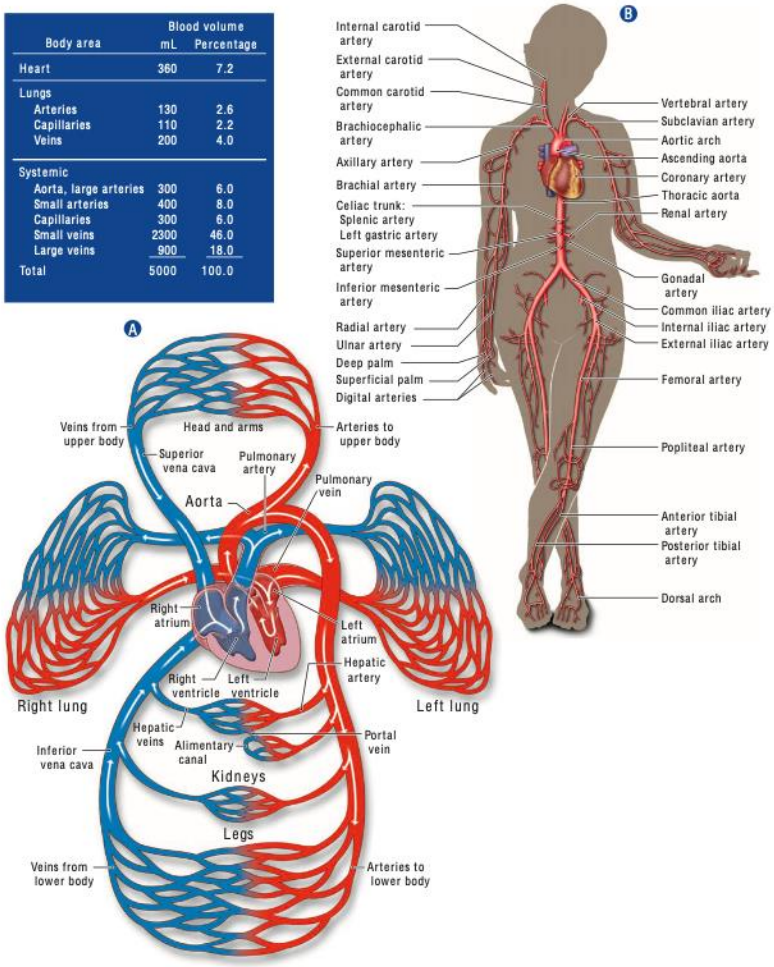


FIGURE 1. Cardiovascular system and its major components (McArdle et al. 2015)

The major pump of the cardiovascular system, the heart, holds approximately 360mL of blood that is about 7.2 % of the total blood distribution. Majority of the relative blood distribution goes to the system circulation, which is composed of veins (64 %), large and small arteries, including the aorta, (14 %) and capillaries (6 %). Vasoconstriction and vasodilation of the arterioles control the amount of blood delivered to each organ (Smith & Fernhall 2011).

Structure and function of blood vessels, specifically arteries, vary across the arterial tree. The aorta, is the largest artery in the body. The rest of the large arteries are carotid, brachial, radial, and femoral. Smaller arteries, with diameter ranging from 150-300 μm, lie distal to the heart and function in microcirculation. The large arteries have distinct structural layers compared to the smaller arteries to exert conduction and compliance function. Prior to distribution, blood is ejected by the heart through the left ventricle entering the aorta and the subsequently to other large arteries. In this case, distensibility and pulsatility of the aorta is vital as it experiences high pulsatile pressure and continuous shear stress. (Chirinos 2012a)

2 ARTERIAL STIFFNESS

Arteries are large conduits of blood vessels responsible for taking blood to the organs and tissues. They have three distinct layers with separate function and composition. Figure 2 shows the schematic histological arrangement of the three layers.

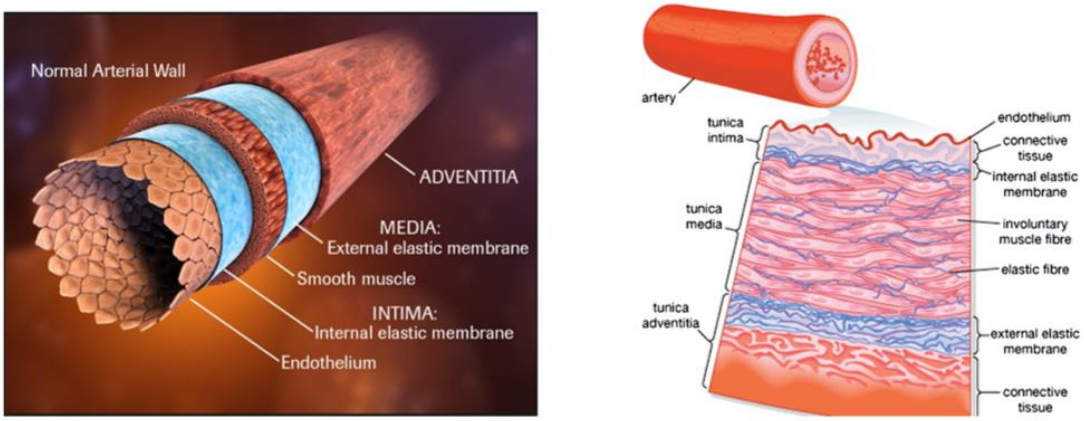


FIGURE 2. Anatomy of the arterial wall (Fortier et al. 2014).

Tunica adventitia, the outermost layer, is composed of connective and elastic membranes and attached to surrounding tissues. The thickest layer, tunica media, consists of concentric organization of musculo-elastic complexes, mainly intertwined vascular smooth muscle cells (VSMC). Media is enveloped by an internal and external membrane separating it from the inner and outer layers. For arteries, the tunica media provides integral support and allows vasoconstriction and vasodilation. This elastic ability of large arteries defines arterial compliance, which decreases as blood pressure (BP) increases. The innermost layer, tunica intima, is made up of squamous epithelial cells enveloped by an internal elastic membrane and connective tissue. (McArdle et al. 2015) Of the three, arterial stiffness, the opposite of arterial compliance, depends on the macrostructure and geometry of tunica media.

2.1 Definition

Arterial stiffness is defined as the decrease in distensibility of arteries (Lacolley et al. 2017). The pulsatile nature and distensible property of the aorta is characterized by the windkessel function of the aorta (Figure 3). The aorta and downstream large arteries adjust to the left ventricular stroke volume during systole (Belz 1995). The left ventricle (left side of the

diagram) ejects blood of about 60-100mL (100 %) into the aorta, where it is partially 'stored' (50 %) and the other 50 % goes directly down and ensures continuous supply to the peripheral circulation. During diastole, the aorta acts as a secondary pump, passively contracting and generating pulse waves downstream, to eject the rest of the stored blood volume into the system. This interplay during systole-diastole shows the elastic storage capacity of the aorta, known as the Windkessel theory (Belz 1995).

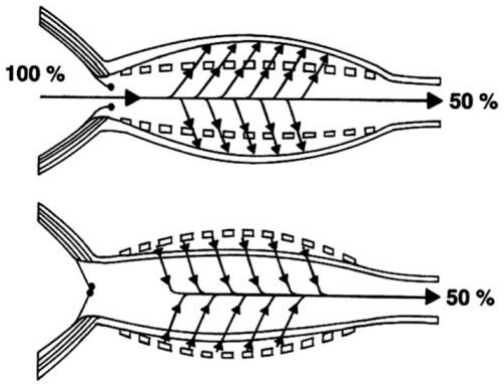


FIGURE 3. Windkessel model of aorta (Belz 1995).

Interchangeably denoted by aortic stiffness, this resistance to elastic deformation of the artery affects the ventricular afterload, causing aortic systolic blood pressure rise (Chirinos 2012b). In each cardiac cycle, the left ventricular ejection of blood traverses the aorta, generating a pulse wave and increasing the luminal pressure of the ascending aorta during early systole. If the proximal wall of the aorta is stiff, it causes an increase in the systolic pressure, leaving a wide gap between systolic blood pressure (SBP) and diastolic blood pressure (DBP). This leads to higher mean arterial pressure (MAP), taken from DBP and pulse pressure, which is difference between SBP and DBP. Elevated SBP, PP, and MAP are clinical manifestations of arterial stiffening (Angoff et al. 2021; Chirinos 2012b; Zieman et al. 2005).

Stress and strain are key elements to the understanding of distensibility. Stress is the applied force on a body. Strain represents the corresponding deformation as a response to the stress. In the case of hemodynamics, shear stress of blood flow is encountered by arterial walls. In cylindrical walls of conduits like arteries, the transmural change in pressure, where the intraluminal pressure caused by increased blood volume exceeds extraluminal pressure, adds pressure to the arterial walls, producing circumferential tension (stress) and lengthening (strain) (Chirinos 2012b). The ratio of tension and deformation is represented by the Young's elastic

modulus E. Hooke's law states that, in Hookean materials, the amount of deformation of an elastic object is proportional to the force applied to it. Because the arterial wall has a diverse molecular and mechanical composition, the arterial wall is not a Hookean material, thus, elastic modulus is curvilinear (Figure 4). The incremental E varies across segments of the dotted black line. For example, the elastic modulus from segment O to A is different, and lower, compared to segment AB; elastic modulus of AB is different and less than that of BC. This is important when assessing arterial stiffness in vivo. The Hookean nature of arterial walls reflects the progressive stiffening of the arterial wall. Hence, when interpreting arterial stiffness in studies, the increasing stress-strain ratio depend on the 'distending' pressure applied to the walls at different levels of MAP. (Chirinos 2012b)

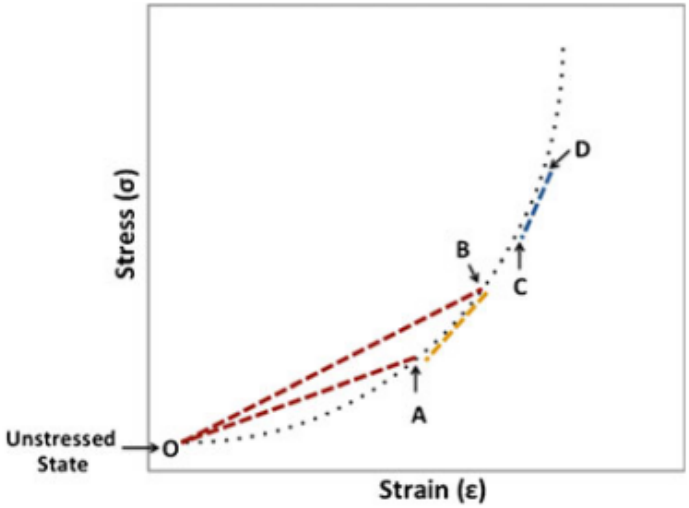
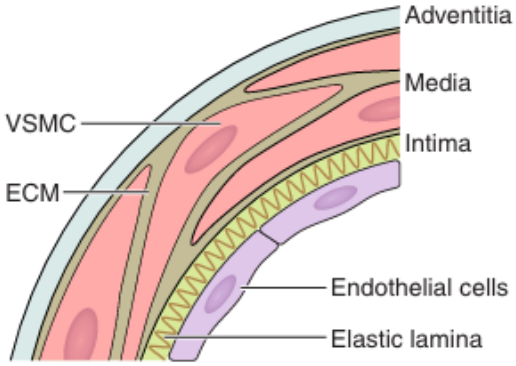


FIGURE 4. Stress-strain relationship in arterial walls.

Arterial stiffness is an independent biomarker associated with cardiovascular diseases and has high correlation with cardiometabolic syndrome. The stiffening of large arteries highly associates with changes in circulation and blood pressure that eventually leads to pathological vascular modifications (Angoff et al. 2021; Chirinos et al. 2019). This clinical significance of assessing arterial stiffness will be explored in the proceeding sections.

2.2 Mechanisms of Arterial stiffness

There are several molecular and cellular causes of arterial stiffness. Distension is a function of the architecture of the tunica media. It is due to changes in the structural components of the arterial wall, mainly the crosslinks between collagen and elastin in the tunica media and tunica intima. Because of advance aging process and pathological reasons, these structures, as well as extra cellular matrix (ECM) are damaged and changed in number, (Lacolley et al. 2017; Zieman et al. 2005). ECM metalloproteinases are collagenolytic enzymes that are affected with aging and consequently degrading existing ECM. As a protective mechanism, newly synthesized ECM often produces elastic fibers in lower numbers and increased in collagen content. This then results to changes in architecture of the tunica media (Lacolley et al. 2017).



FUGURE 5. Schematic diagram of the arterial wall and the changes in its layers (Lacolley et al., 2017)

One of the probable mechanisms underlying arterial stiffness in type 1 and 2 diabetes is the formation of advanced glycation end (AGE) products. An increase in abnormal fiber distribution and stiffer collagenous structures, contributing to weak ECM, is associated with increased level of AGE products (Lacolley et al. 2017; Zieman et al. 2005). Schram and colleagues (2005) investigated measures of arterial stiffness and pulse pressure in men with type 1 diabetes and found a strong association with AGE. AGE's also induce calcification of vascular smooth muscle cells (Tanikawa et al. 2009). Vascular calcification is a pathological process occuring in many cardiovascular diseases such as hypercholesterolemia, diabetes and atherosclerosis (Vattikuti & Towler 2004). Tanikawa and colleagues showed the osteoblast-like differentiation of VSMC mediated through the receptor for AGE (RAGE)/pr8 mitogen-activated protein kinase (MAPK) signaling pathway.

Role of endothelial dysfunction and nitric oxide (NO) imbalance are also evident in arterial stiffening. Nitric oxide is produced by the endothelium that is responsible for vascular smooth muscle relaxation. The enzyme NO synthase (eNOS) synthesizes NO, which cleaves NO from the amino acid L-arginine. Production of NO is regulated by shear stress and receptor-bound agonists. (Smith & Fernhall 2011). AGE-induced reduction of eNOS may result to endothelial dysfunction. Biao et al. (2003) determined the effects of albumin AGE-modified by glucose in both in vivo and in vitro using animal models on aortic rings and human umbilical vein endothelial cells. They found that glucose-derived AGEs inhibited eNOS activity, causing serine phosphorylation of the enzyme (Biao et al. 2003). The reduced production of NO from impaired eNOS activity causes reorganization of the cellular and extracellular components of the vascular structure. This abnormal vascular remodeling eventually leads to endothelial dysfunction that occurs in many diseases such as hypertension, arteriosclerosis, and atherosclerosis (Rudic & Sessa 1999). Increase in shear stress on arterial wall due to exercise hyperemia is an acute response to aerobic exercise training. During physical activity, endothelial cells release NO, which modulates vasodilation that induce relaxation of VSMC and increase regional blood flow (McArdle et al. 2015). On the contrary, inhibition of NO pathway using inhibitors of NO epoxygenases in hand skin heating trial of Bellien and colleagues (2010) showed arterial wall stiffening. Based on their trial, release of NO regulates arterial stiffness by the endothelium.

2.3 Risk factors

Aging is one of the most remarkable risk factors of arterial stiffening that has been studied extensively. Arterial stiffness worsens with advancing age is characterized by stiffening across the arterial tree and changes in organization of elastin and collage in tunica media, wherein elastin degrades and collagen fibers (Bruno et al. 2020; Lacolley et al. 2017; López-Otín et al. 2013). In Table 1, normotensive individuals with optimal blood pressure aged less than 30 years of age have a mean pulse wave velocity of 6.1m/s, which increases around 49 as they reach sixty years old (Angoff et al. 2021)

TABLE 1. PWV values stratified in different age groups and blood pressure categories (N=11,092) (Angoff et al. 2021).

Age category (years)	Blood pressure category				
	Optimal	Normal	High Normal	Grade I HTN	Grade II/III HTN
PWV as mean (±2SD)					
<30	6.1 (4.6–7.5)	6.6 (4.9–8.2)	6.8 (5.1–8.5)	7.4 (4.6–10.1)	7.7 (4.4–11.0)
30–39	6.6 (4.4–8.9)	6.8 (4.2–9.4)	7.1 (4.5–9.7)	7.3 (4.0–10.7)	8.2 (3.3–13.0)
40–49	7.0 (4.5–9.6)	7.5 (5.1–10.0)	7.9 (5.2–10.7)	8.6 (5.1–12.0)	9.8 (3.8–15.7)
50–59	7.6 (4.8–10.5)	8.4 (5.1–11.7)	8.8 (4.8–12.8)	9.6 (4.9–14.3)	10.5 (4.1–16.8)
60–69	9.1 (5.2–12.9)	9.7 (5.7–13.6)	10.3 (5.5–15.1)	11.1 (6.1–16.2)	12.2 (5.7–18.6)
≥70	10.4 (5.2–15.6)	11.7 (6.0–17.5)	11.8 (5.7–17.9)	12.9 (6.9–18.9)	14.0 (7.4–20.6)
PWV as median (10th–90th percentile)					
<30	6.0 (5.2–7.0)	6.4 (5.7–7.5)	6.7 (5.8–7.9)	7.2 (5.7–9.3)	7.6 (5.9–9.9)
30–39	6.5 (5.4–7.9)	6.7 (5.3–8.2)	7.0 (5.5–8.8)	7.2 (5.5–9.3)	7.6 (5.8–11.2)
40–49	6.8 (5.8–8.5)	7.4 (5.3–8.2)	7.7 (6.5–9.5)	8.1 (6.8–10.8)	9.2 (7.1–13.2)
50–59	7.5 (6.2–9.2)	8.1 (6.7–10.4)	8.4 (7.0–11.3)	9.2 (7.2–12.5)	9.7 (7.4–14.9)
60–69	8.7 (7.0–11.4)	9.3 (7.6–12.2)	9.8 (7.9–13.2)	10.7 (8.4–14.1)	12.0 (8.5–16.5)
≥70	10.1 (7.6–13.8)	11.1 (8.6–15.5)	11.2 (8.6–15.8)	12.7 (9.3–16.7)	13.5 (10.3–18.2)

Modified from Reference Values for Arterial Stiffness (31).
HTN, hypertension; SD, standard deviation.

Age-related rise in BP is seen to be one, specifically the predominance of early systolic hypertension and increase in prevalence of hypertension with age in industrialized societies. In the Framingham Heart study where 2036 participants (43.7% men) were examined for hemodynamic patterns, slow progression of hemodynamic parameters, namely SBP, DBP and MAP, from the age 30 to 50 years old is manifested with the peripheral vascular resistance and its association to aging (Franklin et al. 1997).

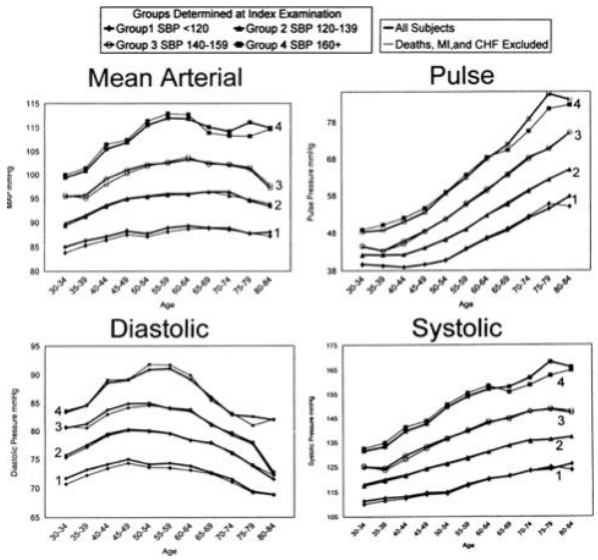


FIGURE 6. Measured pulse rate, systolic pressure, diastolic pressure, and mean arterial pressure in the Framingham heart study (Franklin et al., 1997).

While aging primarily affects structural integrity of arteries leading to compromised arterial compliance, physical inactivity attenuates arterial function. Regular physical activity and exercise is linked to reduced risk of having cardiovascular diseases. Seals and colleagues have shown the benefits of habitual exercise to arterial health. After a moderate intensity aerobic exercise of brisk walking for twelve weeks, middle-aged and older participants improved carotid artery compliance and endothelial function. The study also demonstrated the improvement in blood flow in lower extremities of the participants. (Seals et al. 2008)

Association between arterial stiffness and sex is confounded with age and other risk factors. The interaction between these two factors tend to deviate starting puberty where pre-pubescent males have lower mean PWV compared to the female counterparts. This is reversed in post-puberty age. Rossi and colleagues (2011) explored the biomechanical differences of arterial wall between males and females. Body size and hormones play a significant differentiation between the two sexes, as females have generally shorter stature, which is related to possibility of coronary artery disease. Arterial length, which is correlated with height, is also a component of arterial wave reflection and pulse wave velocity. Generally taller men possess earlier wave reflection to the aorta during systole compared to women, explaining the increased pulse pressure in older women (Rossi et al. 2011). In the Jackson heart study investigating clinical correlates of arterial stiffness in black men and women, adult men have higher cfPWV and women have steeper rise in cfPWV and forward wave amplitude for ages 60 and above (Tsao et al. 2018). Additionally, the authors concluded that there is an association between age and MAP in women than in men.

2.4 Measuring arterial stiffness

Pulse wave velocity, clinically known as PWV, is the rate of propagation of blood pulse waves through the arterial system. It is defined as the speed, measured in meters (m/s) or centimeters per second (cm/s), at which these blood pulse waves are generated after systolic contraction. It provides evaluative information about the elastic properties of the arteries. (Nabeel et al. 2020). Regional PWV is derived from dividing the distance between two different arteries or pulse sites, eg. carotid and femoral arteries, over the time difference between the foot of pulse

waveforms generated by each pulse point (Chirinos 2012b). Regional PWV estimates average PWV over a long segment that might have varying elastic property along the length of interest and does not provide accurate assessment on peripheral arteries. This limitation calls for local pulse wave velocity estimations measured by invasive or imaging techniques.

The gold standard estimate of arterial stiffness in clinical setting is the carotid-femoral PWV (cfPWV). It measures the distance between carotid and femoral pulse points divided by the time delay between two waveforms from carotid and femoral arteries (J. B. Park et al. 2022; Pereira et al. 2015). Recordings of temporal pulse waveforms and superficial distance between strong carotid and femoral pulse sites are used. PWV is calculated as the D/T, where D is the direct arterial distance and T is the time delay between foot of the waveforms (Figure 7a and b).

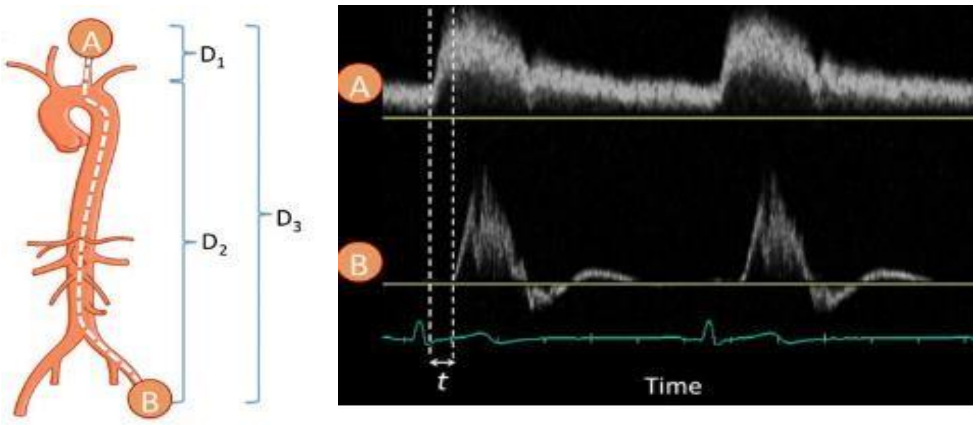


FIGURE 7. a. direct distance between carotid (A) and femoral (B) is measured superficially over the skin of the subject. b. time interval, t, between the foot of waveforms measured at the carotid and femoral pulse sites (Chirinos 2012).

In a more recent study by Angoff and colleagues (2021), 11,092 Europeans were measured to draw reference values as shown in Table 1. For people with mean age less than 30 years old and are normotensive, the mean PWV is 6.6m/s (2SD: 4.9-8.2). AoPWV changes with increasing age, with mean PWVof 11.7m/s for people aged more than 70 years old. Hypertension demonstrates high association with arterial stiffening as illustrated by higher PWV values. Consensus on reference values for Asian population has been proposed by Park and colleagues (2022). CfPWV of greater than 10m/s is abnormal and can inflict different cardiovascular risks to the individual. Additionally, for every 1m/s increase in measured cfPWV, there is 14-15 % chance of CV events leading to disease or mortality.

Another biomarker of clinical importance is the augmentation index, AIx. AIx is the ratio of the augmentation pressure (the difference between systolic blood pressure and first pressure wave) and pulse pressure (the variance between systolic and diastolic blood pressure). It is the contribution of pressure wave reflection to arterial pressure, seen as the difference between the amplitude of first and second systolic in the pulse waveforms. AIx is affected by age, SBP, heart rate, left ventricular ejection time. (Angoff et al. 2021) In patients with coronary artery disease and major adverse cardiovascular events such as unstable angina, acute myocardial infarction, or stroke, high Aix was associated with increased mortality (Chirinos et al. 2005).

2.5 Clinical Significance

Clinicians, medical doctors, and public health practitioners have long established the prognostic value of arterial stiffness assessment in cardiovascular health. Previous studies show the association of arterial stiffness to the development of cardiometabolic disorders and metabolic syndrome. Increased arterial stiffness is strongly linked to hypertension, atherosclerosis, cardiovascular events, and metabolic dysfunction.

Hypertension is highly correlated with arterial stiffness in most studies. In the longitudinal Framingham heart study, arterial stiffness was measured in 7283 subjects and long-term follow-ups showed that increase in carotid-femoral PWV was measured in participants who developed cardiometabolic diseases (hypertension and diabetes mellitus), cardiovascular diseases, (coronary heart disease, stroke and heart failure) and chronic kidney disease (Vasan et al. 2022). Kaess and colleagues (2012) thoroughly investigated the relationship between vascular stiffness, central hemodynamics, and blood pressure in their comprehensive longitudinal cohort study. Primary outcomes are measures of blood pressure and incident hypertension. Three parameters of vascular stiffness were measured – cfPWV, forward wave amplitude, and augmentation index. The main findings suggest that all three measures of vascular stiffness were associated with high risk of incident hypertension (Kaess et al. 2012). Kim et al. (2007) argued that the blood pressure is a contributor to PWV. They used coronary angiography in174 normotensive and untreated hypertensive middle-aged and elderly individuals to evaluate the role of BP on PWV. In the first and third step of multiple regression analysis, the results showed that SBP and MAP were less strong predictors, while PP was a strong predictor in the second. In the analyses, PP remained correlated with aoPWV ($p=0.154$) (Kim et al. 2007). Similarly in

a large cohort study on the relationship of arterial stiffness and hypertension, the probable cause of increased arterial stiffness was the distending pressure instead of structural changes (Arnett et al., 2000). The researchers argued that the hypertension-associated stiffening was a temporary result of an upward shift in volume-pressure curve.

Metabolic syndrome (MetS) is a combination of cardiometabolic risk factors in individuals characterized as overweight or obese and high risk of atherosclerotic cardiovascular diseases and diabetes (Ehrman et al. 2013). Clinical criteria include body composition, lipid profile, blood pressure, and blood glucose. Body composition is depicted in many clinical measurements such as body fat and body fat percentage and waist or waist to hip ratio, which illustrate association between adiposity and cardiometabolic outcomes. Blood serum is analyzed to see levels of triglycerides, eg. high-density lipoprotein (<40mg/dL in males and <50mg/dL in females) and cholesterol (>150mg/dL) (Hayashi et al. 1987). Elevated fasting glucose, >100mg/dL, is an alternative indicator of high risk. Lopes-Vicente et al. (2017) studied the clustering of cardiometabolic risk factors and their relationship with arterial stiffness in 64 patients diagnosed with MetS. MetS risk factors, grouped and used for analyses, were waist circumference, triglycerides, high-density lipoprotein cholesterol, systolic blood pressure, and blood glucose. Non-invasive PWV measurements were obtained using Complior. Using multivariate analysis on groupings of 3, 4, and 5 MetS risk factors, results showed that age, SBP, and triglycerides are the strong predictors of PWV (Lopes-Vicente et al. 2017). This confirms findings from the previous study of Vyssoulis et al (2010) demonstrating the differential effects of clustered MetS risk factors. The more or higher the MetS risk factors present, the greater the impairment in blood pressure, blood glucose, triglycerides, and cholesterol levels, and the higher the resulting aortic stiffness (Vyssoulis et al. 2010). Additionally, independent of blood pressure, race, and age, PWV was elevated in obese and overweight individuals, patients with hypercholesterolemia, Type 2 diabetes, and dyslipidemia (Angoff et al. 2021; Chirinos et al. 2019; Hayashi et al. 1987; Kresnajati et al. 2022; Reiner et al. 2019; Safar et al. 2006).

Blood serum biomarkers are also associated with arterial stiffness allowing further insight into the mechanisms of this phenomenon. Growth factors (GFs), specifically insulin-like growth factor (IGF),have a vasodilatory effects via NO-mechanism which involves arterial wall components endothelial cells and VSMC, thus maintaining balance of eNOS and overall

endothelial health (Asahara et al. 1995; Delafontaine et al. 2004; Isonevic et al. 2003). IGF-1 was shown to stimulate expression of elastin gene in aortic development (Wolfe et al. 1993). IGF-1 levels are negatively associated with cfPWV and it's been shown that low levels of insulin-like growth factor 1 (IGF-1) are associated with arterial stiffness (Ronconi et al. 2005). Vascular endothelial growth factor (VEGF) increases tissue vascularization, counteract arterial stiffening, and inhibits apoptosis of vascular smooth muscle cells, that could collectively enhance peripheral blood perfusion, contribute to lower cfPWV, and reduce mean arterial pressure (Lacolley et al. 2017; Rudic & Sessa 1999; Tomiyama et al. 2018) The links between growth factors and hemodynamic indices were described in the study of Zachariah et al (2012). 3496 subjects from the Framingham heart third generation cohort were analyzed for arterial stiffness using applanation tonometry and circulating blood concentrations of VEGF and IGF. Using multivariate linear regression analysis, main findings of the study illustrated the negative association of IGF-1 to cfPWV and mean arterial pressure at $p<0.01$ and in contrast VEGF was shown to be positively associated with cfPWV and MAP ($p<0.02$) (Zachariah et al. 2012).

Another biomarker associated with arterial stiffness include high-sensitive C-reactive protein (CRP), shown to be elevated with inflammation, increased arterial stiffness, insulin resistance, and markers of atherosclerosis (Effoe et al. 2015; Lestariningsih, L et al. 2019).

3 ARTERIAL STIFFNESS AND EXERCISE

As it is known, aging and poor lifestyle largely contribute to the development of arterial stiffness. Additionally, physical inactivity has a direct effect on 'vascular conditioning' that likely influences cardiovascular risk (Thijssen et al. 2010). Epidemiological reviews have shown that increase in physical activity participation, contributing to improvements in aerobic capacity, is associated with low risk of cardiovascular diseases and low mortality rate. Interventional studies have also been concerned with the acute responses and chronic adaptations on vascular and hemodynamic parameters to different aerobic and resistance exercises training. This is the reason several scientific organizations prescribe exercise training to mitigate future cardiovascular events.

3.1 Effects of aerobic and resistance exercise on arterial stiffness

Contrasting results on the impact of resistance training on arterial stiffness were documented. Previous studies have shown that resistance exercises have decreased arterial compliance. Yoon et al. (2010) investigated the impact on increased arterial stiffness in healthy young men through a short-term resistance exercise program. The results showed that HR (59.2 ± 9 vs. 80.4 ± 10.6 bpm), AIx (−6.3 vs. −2.6), and cfPWV were all significantly increased after 20 min post-execise of the exercise group compared to the control group. In a more recent study by Kingsley et al (2016) the cfPWV and heart rate response increased after an acute bout of free-weight, whole-body resistance exercise resistance-trained individuals and thus showed that resistance training can increase arterial stiffness (Kingsley et al. 2016). In contrast, Heffernan et al (2007) found that acute resistance exercise did not significantly change arterial stiffness. The study protocol investigated the central and peripheral arterial stiffness and compared PWV measures on both legs, one was a control, non-exercising leg and the other was the exercising leg. Authors showed that there was no change in central arterial stiffness and the non-exercised leg. The results from these studies suggest that there is no consensus yet on this subject and further experimental studies are needed to determine acute and chronic responses of resistance exercise on arterial stiffness.

Endothelial dysfunction is an early biomarker of arteriosclerosis, or the hardening of arteries. It is also associated with arterial stiffening and systemic arterial hypertension, which is an apparent cardiovascular risk factor. Exercise-induced hyperemia occurs when there is a rise of

muscle blood flow due to redistribution of blood to the working muscles. Repeated exposure to high shear stress in the vascular wall during exercise-induced hyperemia is attributed to improvements in endothelial function (Smith & Fernhall 2011). In many studies on effects of exercise on vascular function, endothelial function is assessed by flow-mediated dilation (FMD). Siasos and colleagues (2016) investigated the effects of continuous moderate intensity and high intensity interval aerobic exercises on twenty healthy men. The methodology used to assess endothelial function involved FMD in the brachial artery and carotid-femoral and femoral-dorsalis pedis PWV were measured to measure arterial stiffness. Both continuous moderate intensity and high intensity interval aerobic exercises significantly improved FMD (6.37 ± 1.48 vs. 8.57 ± 2.55 %, $p < 0.001$ and 5.95 ± 1.78 vs. 8.48 ± 2.60 %, $p < 0.001$ respectively), so as the measured femoral-dorsalis PWV at $p<.005$. However, there was no significant change in cfPWV. The authors showed that both aerobic exercise modalities could improve endothelial function (Siasos et al. 2016). In a more recent experimental protocol, Pedralli et al. (2020) examined the effects on endothelial function via FMD and blood pressure using three different exercise types: aerobic exercise, resistance exercise, and combined aerobic and resistance training. Forty-two prehypertensive or hypertensive participants (SBP>130mmHg or DBP>80mmHg) were randomly segregated into the three different groups. After eight weeks of exercise training, blood pressure was reduced in all groups. SBP was decreased by -5.1mmHg in aerobic exercise group, -4.00mmHg decrease in SBP in resistance exercise group, and -3.2mmHg in DBP in the combined exercise group. FMD improved in all groups **(**+3.2 **% (**95 % CI 1.7, 4.6) ($p < 0.001$) in AT; +4.0 % (95 % CI 2.1, 5.7) ($p < 0.001$) in RT; and +6.8 % (95 % CI 2.6, 11.1) ($p = 0.006$). This showed that different exercise modalities posed positive changes in endothelial function and blood pressure of prehypertensive and hypertensive individuals.

3.2 Effects of exercise on the cardiovascular function and structure

Maximal oxygen uptake (VO_{2max}) or the measure of how the cardiorespiratory system can deliver oxygen throughout the body is shown to increase with aerobic exercise. Moreover, aerobic exercises also enhance stroke volume and cardiac output, Q, and blood perfusion in the skeletal muscles. Heart rate is reduced with endurance training, thus decreasing workload of the heart at homeostatic and exercise conditions. These cardiac adaptations may partly be due to exercise-induced vascular and peripheral adaptations. In normotensive population, SBP and

DBP are slightly but significantly reduced after exercise. Noteworthy blood pressure changes are seen in hypertensive individuals where aerobic exercise has a more blood pressure-reducing impact. Vascular resistance is reduced, and vascular tone is improved after endurance exercise training. These changes impact central and peripheral blood flow. During low to medium intensity exercise, low blood flow happens, which is possibly a result of smaller metabolic vasodilator signaling. However, during high intensity exercise, either lowered sympathetic vasoconstriction or elevated vasodilation occurs. This event is mainly due to reduced activity of the muscle sympathetic nerve during high intensity exercise. Vasodilation is also affected by training. Mechanisms of the endothelial function impact vasodilation. Hence, aerobic training promotes changes in endothelial function. One method to demonstrate this is through flow-mediated vasodilation. Vascular occlusion is performed on an extremity usually the arm or leg, wherein blood is occluded for a certain period of around 5-10 minutes. Upon reintroduction of blood, high shear stress is experienced by blood vessels due to high blood flow, inducing vasodilation. This method is seen under a Doppler ultrasound imaging technique (Smith and Fernhall 2011).

Aerobic exercise also stimulates vascular remodeling, arteriogenesis and angiogenesis. Angiogenesis is defined as the development of new blood vessels (Zieman et al. 2005). In a study investigating whether arterial remodeling occurs in the femoral artery after three months of regular endurance exercise, Dinenno and colleagues found out that the luminal diameter of the femoral artery increased by 9 % in 22 men (8.82±0.18mm vs 9.03±0.13mm) and the femoral intima-media thickness was reduced by 15-20 % (0.65±0.05mm vs 0.56±0.05mm) at $p<.001$. This serves as a potential evidence to endothelium-dependent exercise-induced changes in the arterial structure (Dinenno et al. 2001). Charifi and colleagues (2004) demonstrated the training-induced changes on microvascularization in older men. Capillary-to-fibre (C/F) ratio, as well as the proportion of length of capillaries in contact with the fibers to fiber perimeter (LC/FP), increased by 18 % and 56 % ($p<.001$) after 14-weeks of 45-minute ergometer cycling (Charifi et al. 2004). The sprouting of new capillaries from old ones will provide greater gas exchange and the increase in LC/FP will improve diffusive capacity. In an animal model showing vascular adaptation, inhibition of collateral vessel enlargement and blood flow were seen in vascular endothelial growth factor (VEGF) receptor-blocked exercise-trained and sedentary rats (Lloyd et al. 2005). This potentially translates to dependency of arteriogenesis on VEGF-R signaling. The study also showed the importance of enhanced mitochondrial

ribonucleic acid (mRNA) expression of VEGF family and endothelial nitric oxide (NO) synthase in blood vessel enlargement and angiogenesis.

Adaptations in the cardiovascular system are also documented after acute and chronic resistance training. First are the morphological changes in the heart. Exercise-induced cardiomegaly was then associated with pathological left ventricular hypertrophy. However, the 'athlete's heart' is a condition in which the heart increases its size due to structural adaptation of the left ventricle, permitting rise in stroke volume and cardiac output during exercise. Specifically, the left ventricular septal wall thickness significantly increases in resistance-trained athletes. In contrast to chronic aerobic exercise-induced bradycardia, changes in heart rate were small or insignificant after resistance training. For acute bouts of resistance training, systolic and diastolic function are enhanced, leading to large increase in blood pressure as a result of active sympathetic nervous system. Vascular changes depend on the intensity of resistance exercise. Total peripheral resistance (TPR) lowers down, as in aerobic exercises, to allow blood perfusion in the working muscles. TPR increases as the intensity (1RM) increases that may be due to increase in intramuscular pressure during lifts. However, there are contradicting findings on the effect of resistance exercises on endothelial function. Resistance exercises increase shear stress in the peripheral arteries, resulting to improvements in microvascular endothelial function but this is not seen in large arteries. Cross-sectional studies also have shown that there are no significant differences on arterial stiffness between sedentary and resistance-trained individuals. Furthermore, early studies suggested that long-term resistance exercise training produced less compliant arteries because of the increased vasoconstriction of the smooth muscle. These findings call for more elaborate studies on the differential effects of chronic resistance exercises on humans. (Smith & Fernhall, 2011)

Illustrated in Figure 8, Kresnajati et al. (2022) summarizes the impacts of endurance and resistance exercises on arterial stiffness on the following diagram. It is interesting to explore the dose-response relationship, including novel types, of exercise and arterial stiffness. Because as data collectively suggest with reservations on the side of resistance exercise, aerobic exercise promotes endothelial senescence, insulin sensitivity, and improvement in arterial stiffness. While the transient, and possibly chronic, effects of resistance exercise training negatively impact arterial compliance.

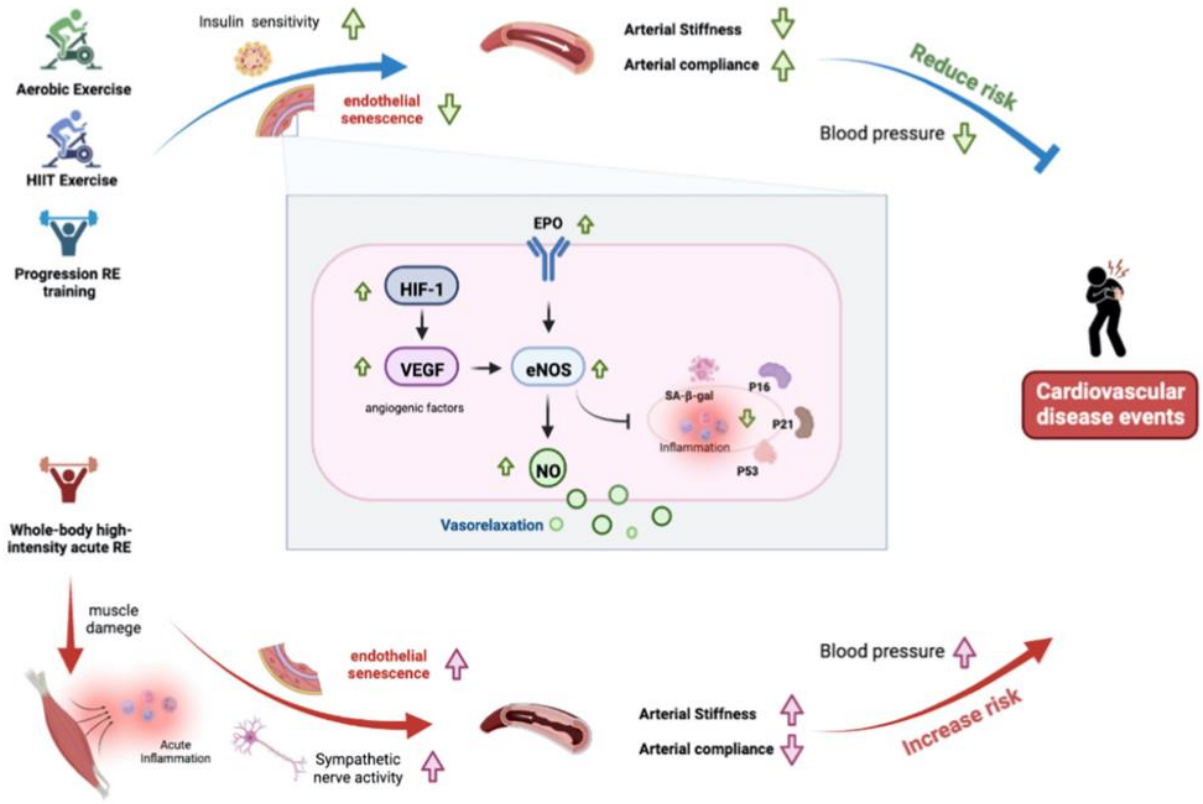


FIGURE 8. Arterial stiffness is impacted by exercise, and the changes depend on the mode of exercise. Aerobic, high intensity interval and pressive resistance exercises improve VEGF-1 and NO bioavailability which induces vasorelaxation. This central mechanism is the main hypothesis on the vascular and hemodynamic adaptation to exercise (Kresnajati et al. 2022).

4 ARTERIAL STIFFNESS, EXERCISE AND CARDIOMETABOLIC SYNDROME

The stiffening of the aorta or large arteries as an independent MetS risk predictor has been established in many cardiovascular events. Physical activity and exercise, on the other hand, have been shown to improve vascular and endothelial functions through several mechanisms. Arterial destiffening and chronic hypotensive effects are centrally evident in previous studies on the effects of exercise training interventions on arterial stiffness. Vascular adaptation seen concurrently in lowering of blood pressure might influence early arterial compliance post-exercise intervention (Figure 9) (Diourte et al. 1999).

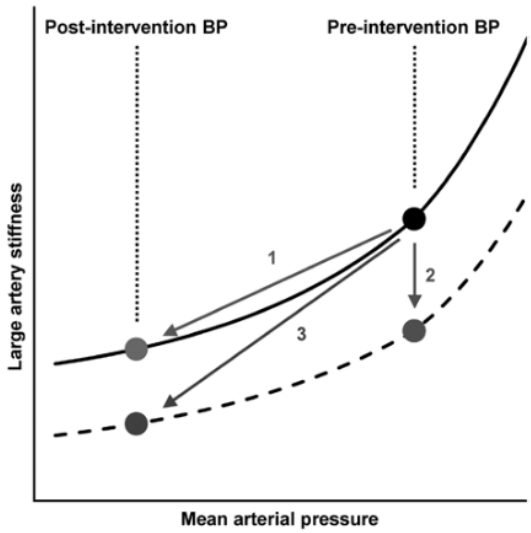


FIGURE 9. Shift (3) in the overall effect of functional and structural arterial compliance. Functional arterial compliance represented by decline in mean arterial pressure (1) Structural destiffening (2) is represented by the downward shift of the stiffness-pressure curve (dashed line).

In a meta-analysis of Lopes and colleagues (2021) that compiled studies on effects of exercise on arterial stiffness in adults with hypertension, fourteen randomized controlled trials (five aerobic exercise intervention, two dynamic resistance exercise intervention, six combined aerobic and resistance exercises) with 642 participants showed that exercise interventions were able to improve PWV and thus improving arterial stiffness in adults with hypertension. Difference in PWV between pre- and post- is -0.76m/s (-1.05 to -0.47), at 95 % C.I. However, chi-squared test showed significant heterogeneity (X^2 = 39.32, p<.001). Further analyses interpreted effect of different exercise modalities on PWV. PWV was improved in aerobic

exercise, combined aerobic and resistance, and isometric resistance exercises, as shown in Figure 10.

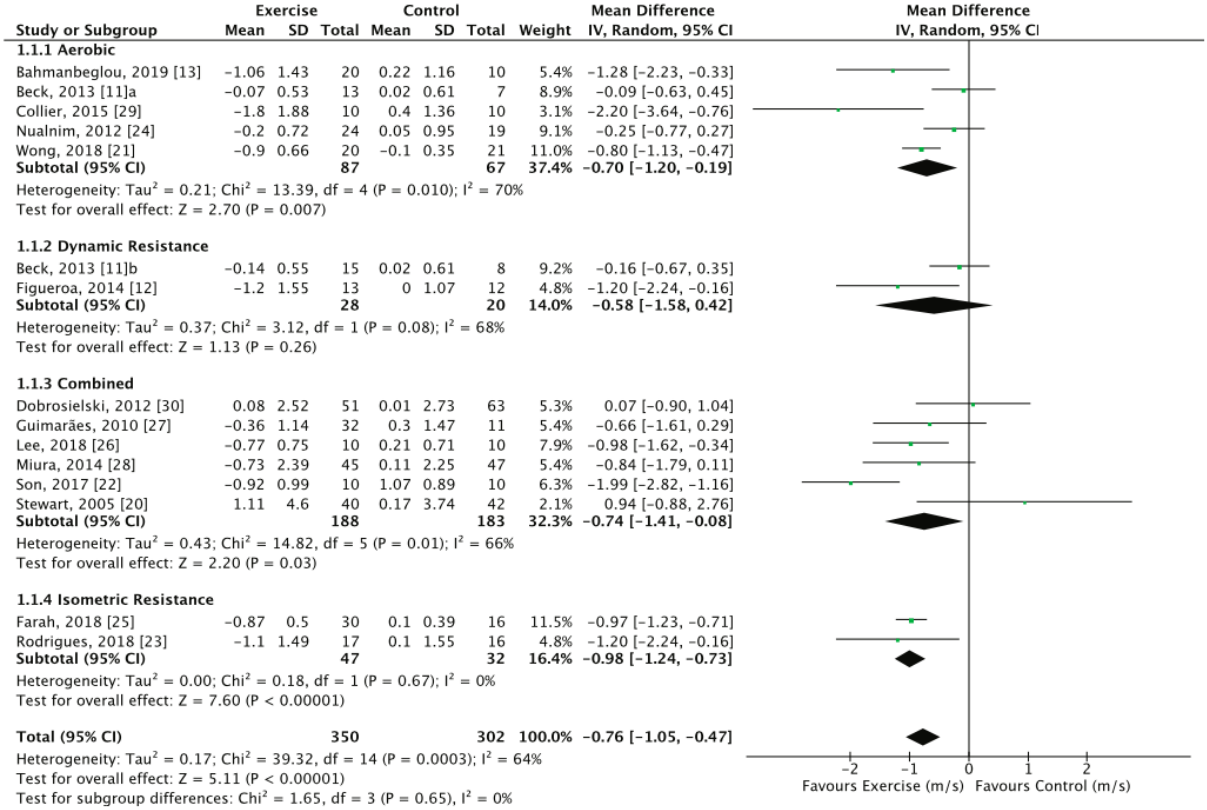


FIGURE 10. Between-group comparison of the effects of different exercise modalities on PWV in m/s. Cl, confidence limits; SD, standard deviation (Lopes et al. 2021).

In population with overweight and obese population, there are still inconclusive data on the improvement of arterial stiffness after aerobic exercise training. Eight clinical trials were included in the meta-analysis made by Montero and colleagues (2014). The study aimed to investigate the effects of aerobic exercises on obese population with body mass index greater than 30. The group recorded values of arterial stiffness parameters such as PWV, augmentation index, and distensibility. The findings showed that arterial stiffness was not significantly reduced by aerobic exercises (standard mean difference -0.17, 95 % CI, p=0.14). The subgroup analyses showed arterial stiffness was decreased in groups with below median values in SBP (p<.01), exercise intensity rating score (p<.01), methodological quality score (p<.01) (Montero et al., 2014). The study was limited to eight to twelve weeks of intervention, where most trials were within 30-60-minute duration of aerobic exercises and intensities recorded were 60-75% HRmax, 60-70 % heart rate reserve, and 64 % VO_{2max}. With this, the group added that the slight significant improvement in both SBP and PWV happened in the low intensity group. At high

intensity, plasma oxidation of free fatty acids (FFA) declines, whereas mobilization and oxidation of FFAs increased at low intensity aerobic exercises (Sidossis L et al. 1997). However in obese and overweight children, exercise training tends to reduce arterial stiffness via PWV measurement and intima-media thickness in subjects with BMI less than 30 (Cheng et al. 2022). Exercise-induced flow-mediated dilation increased in aerobic exercise and high intensity interval training interventions, but with less impact from resistance training. Further analyses showed that only in participants aged 14 years and below were FMD, PWV and intima-media thickness reduced. On the other hand, the EXAMIN AGE study of Deiseroth and colleagues (2019) examined the long-term changes in arterial stiffness of older population (mean age 59±7years), divided into sedentary, healthy sedentary, and healthy active groups. The sedentary group performed 12 weeks of high intensity interval training but did not show any significant improvement in PWV (Pre-intervention PWV= 8.2±1.2m/s; Post-intervention PWV= 8.1±1.1m/s; $p<.05$)

The interplay among the independent risk factors and outcomes in the study of exercise and arterial stiffness and its comorbidities needs a vast discussion. Figure 11 shows the interaction between exercise and its effects on arterial stiffness, as well as the corresponding vascular and cardiac adaptations (Sacre et al. 2014).

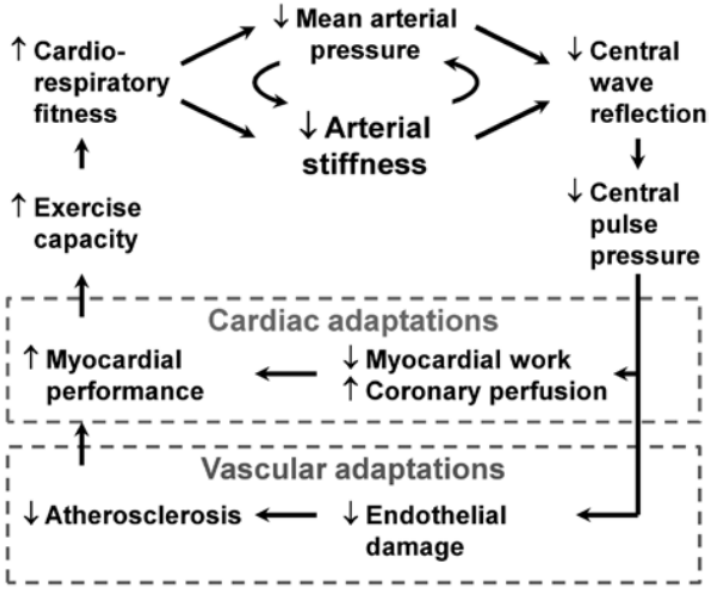


FIGURE 11. Exercise influences cardiorespiratory fitness, promoting improvements in blood pressure and arterial stiffness. This in turn would have positive influences on cardiac and vascular structures that eventually enhance exercise capacity (Sacre et al. 2014).

Multiple mechanisms such as relaxation of VSMC, increased shear stress on the arterial wall, and active enzyme nitric oxide synthase have been attributed to adaptations after aerobic exercise training. Cameron et al. (1994) described the improved arterial compliance and aortic stiffness index in healthy sedentary adults after undergoing four weeks of aerobic exercises. This, however, was suggested as rather functional than structural at the time of study (Cameron et al. 1994). Park and colleagues (2010) were able to demonstrate the influence of combined exercise training on vascular structure and VEGF in obese older women. Their findings showed that after a 12-week combined exercise training composed of yoga, aerobic exercise and resistance band exercise, the subject pool of 20 old obese women showed significant improvements in SBP, VEGF, and LDL-C levels (Park et al 2010).

5 RESEARCH QUESTIONS AND HYPOTHESES

The main purpose of this thesis is to investigate the hemodynamic and vascular adaptations in overweight or obese out-patients after a six-month program of combined aerobic and resistance exercises. Secondary objectives are to compare body composition measurements between pre- and post-intervention program, and to investigate potential correlation between several blood serum biomarkers, which are linked to metabolic syndrome, and measured changes in hemodynamic indices.

Research question 1: Are there changes in the hemodynamic and vascular parameters after a six-month exercise intervention program in patients with cardiometabolic syndrome?
Hypothesis 1: Yes, there will be changes in measured hemodynamic and vascular parameters. Overweight and obese individuals are likely to have stiffening of the arteries and increased pulse wave velocity measurements, regardless of gender or age (Safar et al. 2006). High PWV values indicate cardiovascular disease risk and a prognostic measure of coronary heart disease and stroke in predisposed individuals (Green & Smith 2018; Nabeel et al. 2020). Pulse wave velocity, systolic blood pressure, mean arterial pressure, and pulse pressure are all decreased in previous randomized controlled trials involving overweight and obese population after undergoing exercise intervention (Gong & Liu 2022; W. Park et al. 2020).
Null Hypothesis: There is no significant changes in hemodynamic and vascular parameters of the patients.

Research question 2: Is there a relationship between concentration of blood biomarkers, eg. total cholesterol (TC), high-density (HDL-C) and low-density lipoprotein-cholesterol (LDL-C), triglycerides (TG), and free fatty acid (FFA)] and arterial stiffness of the patients?
Hypothesis 2: The number of metabolic syndrome risk factors, including triglycerides and blood pressure increase arterial stiffness (Lopes-Vicente W. et al. 2017). In addition, three lipid profile variables, LDL, TC, and TG, are positively associated with brachial-ankle PWV measurements (Wang et al. 2020).
Null Hypothesis: There is no relationship established between blood biomarkers and arterial stiffness of the patients.

6 RESEARCH METHODS

6.1 Participants

Participants were out-patient recruits from the Exercise Medicine Clinic (EMC) of Hospital Nova of Central Finland, who voluntary participated in this human patient trial. Eleven (11) subjects completed arteriography measurement, maximal oxygen test, and blood samples were also collected. Subjects were included upon the referral and recommendation of their respective physicians to undergo exercise intervention program and were characterized with cardiometabolic syndrome, who were considered overweight or obese with body mass index greater than 25 Subjects have no preexisting medical conditions and have not participated in regular exercise regimen or with low physical activity. All of them will undergo an exercise program, be tested prior to participation and conduct test measurements after 6-months for follow-up.

6.2 Study design

The experimental design was a six-month, one-arm human patient trial. Participants were prescribed with an exercise therapy (ExT) program. Baseline measurements prior to the start of exercise program and six-month follow-through measurements were performed. Baseline and follow-up measurements were conducted at Liikuntalaboratorio, Faculty of Sport and Health Sciences and were completed on one day with six-month interval. Body composition measurements were collected first, followed by extraction of blood samples, and finally, measurements of hemodynamic variables.

The exercise therapy was individually tailored according to the patient's preferences. Guided exercise sessions were also provided and they were composed of aerobic exercise (cycling on bicycle ergometer) for thirty minutes, resistance exercises (supervised resistance band exercises for 45 minutes), and own home exercises. The voluntary aerobic and resistance exercises were supervised by a physiotherapist or exercise physiologist at the Liikuntalaboratorio.

6.3 Measured Outcomes

On testing days, the following measurements were summarized in Figure 12:

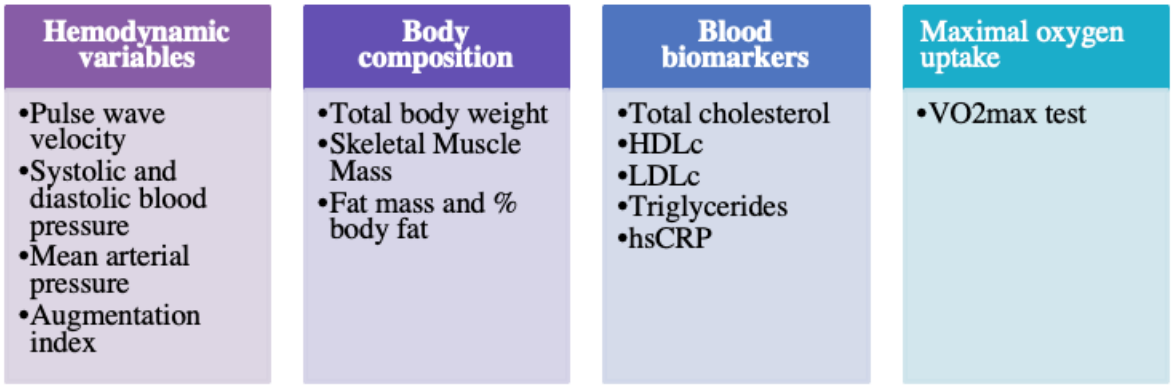


FIGURE 12. List of tests and measurements collected for baseline and follow-up.

Arterial stiffness and other hemodynamic indices

Pulse wave velocity (PWV) is a parameter measured to assess arterial stiffness. Tensiomed Arteriograph (Budapest, Hungary) was used to measure PWV and this device also simultaneously records other parameters such as central blood pressure, mean arterial pressure and the augmentation index. Subjects laid down in a supine position and rest for ten minutes before collection of measurements. After the resting period, a cuff connected to the arteriography device was wrapped around the arm, over the brachial artery. Data was recorded and transferred to a software program on a computer via Bluetooth.

Body composition

Weight, height, lean body mass, fat mass and body fat percentage were measured by dual-energy x-ray absorptiometry and bioelectrical impedance analysis equipment Inbody. Patients were instructed to fast overnight.

Blood biomarkers

Clinical and laboratory recorded parameters include blood serum lipid profile. All collected blood serum will be stored in a safe facility under the supervision of trained staff of the Faculty of Sport and Health Sciences. The following blood biomarkers are subsequently analyzed and quantified: total cholesterol (TC) level, high-densiy lipoprotein (HDL), low-density lipoprotein (LDL) levels, triglyceride (TG), and high-sensitive C-reactive protein.

Maximal Oxygen Consumption

Graded exercise testing was done via treadmill stress test using modified Bruce protocol to obtain maximal oxygen consumption.

6.4 Statistical Analysis

Mean and standard deviation are calculated for each primary dependent variable. To measure the impact of exercise intervention program, paired T-test is used on each identified parameter between baseline and post-ExT measurements. Pearson correlation test is also used to show strength of correlation between selected independent and dependent variables. In case of non-normality, Wilcoxon Signed Rank test was performed.

7 RESULTS

A total of eleven (11) patients participated and completed all required measurements of this study. Table 2 summarizes the participants' characteristics.

TABLE 2: Participants' characteristics before and after 6-month exercise therapy (ExT). Data is represented as means (SD).

Variables	PreExT	PostExT
Age	42.6 (11.4)	43.1 (11.4)
Height (cm)	173.0 (12.0)	172.9 (12.1)
Body weight (kg)	104.9 (14.4)	104.2 (16.5)
BMI* (kg/m^2)	35.0 (3.0)	34.7 (2.9)

*BMI = Body mass index

7.1 Arterial Stiffness

There was a significant improvement in arterial stiffness between pre- and post-6-month of exercise therapy in patients. It was found that the 6-month ExT contributed to the improvement in pulse wave velocity (Table 3). Figure 13 shows individual changes in PWV values after 6-months.

TABLE 3: Measured vascular function variables

Variables	PreExT	PostExT	p-value
PWV (m/s)	8.54 (1.49)	7.75 (1.34)	.009
AIx	25.45 (16.59)	27.06 (17.9)	.497
MAP (mmHg)	91.36 (8.66)	92.82 (10.24)	.479

*PWV = Pulse wave velocity; Aix = augmentation index; MAP = mean arterial pressure

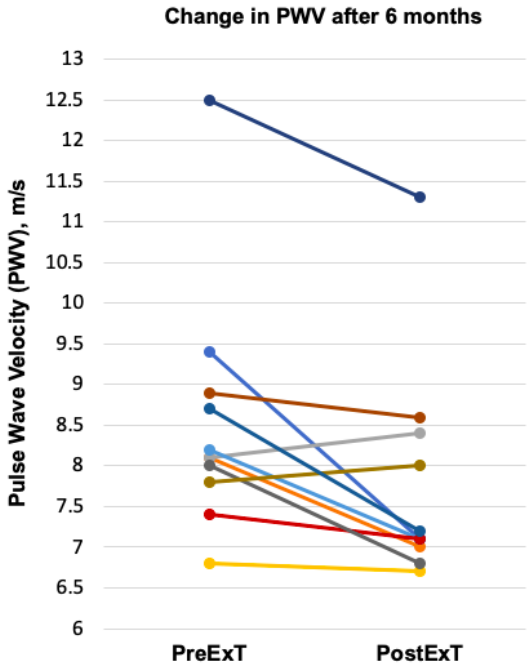


FIGURE 13. Individual PWV scores from baseline to post-ExT

7.2 Body Composition

There was a slight and insignificant decline in body weight (0.72, SD=5.41) pre- and postExT. However, significant changes were recorded for fat mass, body fat percentage, visceral fat range, and skeletal muscle mass.

TABLE 4. Changes in body composition.

Variables	PreExT	PostExT	p-value
Body weight (kg)	104.9 (14.37)	104.18 (16.48)	.669
Fat mass (kg)	43.13 (8.07)	40.02 (8.87)	.035
Body fat percentage (%)	41.38 (7.15)	38.89 (8.05)	.003
Visceral fat range (m^2)	211.39 (43.21)	183.35 (44.21)	.002
Skeletal muscle mass (kg)	34.69 (7.64)	35.83 (8.78)	.042

7.3 Blood pressure

Wilcoxon Signed Rank test for non-normal distribution revealed that there were no significant changes in blood pressure and mean arterial pressure. Pre-post-ExT difference in %change PWV was not associated with post-ExT SBP (r=0.078, p=0.821).

TABLE 5. Hemodynamic variables before and after ExT.

Variables	PreExT	PostExT	p-value
SBP (mmHg)	127.00 (12.69)	129.27 (14.62)	.448
DBP (mmHg)	73.36 (8.63)	74.73 (9.42)	.476
MAP (mmHg)	91.36 (8.66)	92.82 (10.24)	.422

*SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure

Table 6 shows the number of patients under blood pressure classification as per European Society of Hypertension Guidelines (Mancia G. et al., 2024). Table 7 lists the correlation between hemodynamic and blood pressure variables.

TABLE 6. Patients' BP classification

Classification	PreExT	PostExT
Normal BP*	7	6
High Normal BP	2	2
Grade 1 Hypertensive	2	3

*BP = Blood pressure

TABLE 7. Correlation between hemodynamic and blood pressure parameters after 6 months.

Variables	Mean (SD)	PWV	AIx	MAP	SBP	DBP
PWV	7.75 (1.34)	-				
AIx	27.06 (17.90)	0.569	-			
MAP	92.82 (10.24)	0.549	0.650*	-		
SBP	129.27 (14.62)	0.686*	0.654*	0.899*	-	
DBP	74.73 (9.42)	0.372	0.553	0.944*	0.706*	-

*Significant correlation at 0.05 level

7.4 Blood lipid profile

Table 8 below shows the changes in blood lipid profile and inflammatory marker, hsCRP, before and after 6-month exercise therapy. There were no significant changes in the lipidemic

profile before and after ExT. In contrast, a Wilcoxon Signed Rank test, indicated a significant improvement between preExT and postExT hsCRP mean values (z=-1.113, p=0.050). The correlation coefficients between post-ExT PWV and blood lipids are listed in Table 9.

TABLE 8. Changes in blood lipid markers pre- and post-ExT

Variables	PreExT	PostExT	p-value	z-value
Cholesterol (mmol/L)	4.72 (0.75)	4.68 (0.99)	.681	
HDLc (mmol/L)	1.29 (0.49)	1.32 (0.57)	.583	
LDLc (mmol/L)	2.93 (0.48)	2.85 (0.60)	.273	
Triglycerides (mmol/L)*	1.67 (1.02)	1.55 (1.06)	.266	-1.956
hsCRP (mg/L)*	6.06 (8.98)	4.74 (7.75)	.050	-1.113

*Means were not normally distributed and assessed using Wilcoxon Signed Rank test for non-parametric distribution

TABLE 9. Correlation between post-ExT PWV and lipid profile parameters

Variables	PWV	Chol	HDLc	LDLc	Triglycerides	hsCRP
PWV	-					
Chol	0.253	-				
HDLc	0.423	0.883*	-			
LDLc	-0.18	0.873*	0.769*	-		
Triglycerides	0.069	-0.173	0.432	-0.513	-	
hsCRP	-0.129	0.530	00.338	0.359	0.339	-

*Significant correlation at 0.05 level

7.5 Cardiorespiratory fitness

VO2max test revealed that there was a slight improvement in maximal oxygen consumption before the intervention (mean=28.82 ml/kg/min, SD=5.56) compared to after 6-months of exercise therapy (mean=30.16 ml/kg/min, SD=5.63), but they were statistically insignificant at p=0.264.

8 DISCUSSION

The purpose of this thesis was to examine changes in arterial stiffness and metabolic syndrome parameters after a 6-month exercise therapy. Participants were hospital outpatients referred by physicians to undergo an ExT, which was a combination of spinning or cycling in a bicycle ergometer for thirty minutes once or twice a week, supervised resistance band exercises, and home exercises of their choice.

8.1 Improvement on vascular function

The finding of this study demonstrated that exercise training benefited the patient cohort by improving the vascular function in terms of arterial stiffness. The mean baseline PWV was 8.54 m/s whereas the post-ExT PWV significantly improved to 7.75m/s ($p<0.05$). Prior to ExT, this cohort's (age range 30-59 years old) mean PWV was considered elevated compared to normative PWV reference of 6.6-8.4 m/s (Angoff et al. 2011). A decline of 8.81% in mean percent change of PWV was recorded. The widest change recorded was from 9.4 m/s down to 7.10. Positive changes in arterial stiffness after exercise training were comparable to previous intervention studies, combining aerobic and resistance training, had beneficial effect on vascular function of individuals who were overweight or obese, with metabolic syndrome and hypertension (Corrick K.L. et al. 2013; Gong L. & Liu Y 2022; Park W. et al. 2020; Siasos G. et al. 2016). Augmentation index is another surrogate measure of arterial stiffness and systemic vascular resistance (Sakurai M. et al. 2007). Aix is associated with high pulse pressure, abnormal lipid profile, and age. Moreover, AIx is affected by both central and peripheral arterial stiffness (Kelly et al. 1989). Hence, it is possible to have variations in PWV while Aix remained unchanged. There was no significant change in Aix in the present study.

Arterial stiffness is an independent predictor of cardiovascular health (Chirinos J. et al. 2019). A significant decrease of PWV in patients or individuals with metabolic syndrome can be clinically relevant in reducing cardiovascular disease risk. The main mechanism of vascular adaptations to exercise is attributed to repeated exposure to high shear stress during exercise-induced hyperemia (Smith & Fernhall 2011). The results of this study support this hypothesis, however, the prescription of exercise therapy in terms of volume and intensity must be structured to establish a definitive dose-response relationship of the benefits of ExT to arterial stiffness.

8.2 No improvement in blood pressure

Blood pressure is correlated with arterial stiffness with PWV increases progressively as BP increase. (Kaess B. et al. 2012). In the Framingham study, participants with high cfPWV developed hypertension and cardiometabolic diseases after a long-term follow-up (Vasan et al. 2022). It has been shown in this study the high correlation between post-ExT PWV and SBP ($r=0.686$, $p=0.020$).

Aortic stiffening could cause isolated increase in SBP due to the hemodynamic consequence to elevated pulse pressure of aortic root and wall stiffening (Chirinos J. et al. 2019). Kaess and colleagues (2012) also emphasized the probability of bidirectionality of causality of arterial stiffness and systolic hypertension. In the ESC guidelines (2024), a decrease in PWV is a prognostic marker to be considered in managing patients with hypertension. In this study, both SBP and DBP were slightly elevated after 6-months, +2.27mmHg and +1.36mmHg at $p>0.05$, respectively. The number of patients with grade 1 hypertension (SBP 140-159mmHg and up and/or DBP 90-99mmHg) increased from two to three patients. The increase in blood pressure in this study did not agree with previous evidence, showing improvement in both arterial stiffness and blood pressure after combined aerobic and resistance training (Corrick K et al. 2012; Park et al. 2020; Zota I. et al. 2021). The mechanisms by which improvement in arterial stiffness is independent of BP is unclear. Tan and colleagues (2016) demonstrated that increase in arterial stiffness post-exercise did not match corresponding increase in blood pressure, wherein the mediating factor is heart rate. Their study illustrated the negative interaction between blood pressure and heart rate, while heart rate was directly related to cfPWV.

8.3 Changes in blood lipid profile

Endurance and resistance exercise training have been shown to reduce plasma triacylglycerol and cholesterol concentration (Mougios V. 2019). Interventional studies demonstrated the ability of exercise training to lower plasma levels of triglycerides, cholesterol and LDL in untrained individuals and reduce CVD risks.

However, in this study there were no significant differences in metabolic syndrome risk factor parameters between pre- and post-ExT, except hs-CRP with mean difference of 1.32 mg/L at $p=0.050$. This was a similar finding from the intervention of Kondo and colleagues (2006)

where they showed the lower levels of circulating c-reactive protein after seven months, with more frequent and intense exercise training regimen. The current study found lower level of triglycerides, LDL, and cholesterol and an increase in HDL after the six months of exercise therapy but deemed insignificant. In contrast to previous evidence wherein arterial stiffness is associated with lipid profiles, this study showed low correlation between PWV and lipid profile parameters (Park W. et al 2020; Wang L. et al. 2020). The findings failed to support the hypothesis excessive plasma levels of lipids and cholesterol would lead to vascular stiffness (Schram et al. 2005; Zieman et al. 2005). While individual association is not evident in the current study, Lopes-Vicente and colleagues (2017) was able to demonstrate how clustering of metabolic syndrome risk factors could potentially cause arterial stiffening. They showed that those who have altered in triglyceride level, plus high SBP, and age had higher PWV compared a control group. At least three out of five clustered risk factors must be present to be diagnosed with metabolic syndrome. These risk factors defining the operational criteria of having metabolic syndrome are waist circumference, triglyceride levels, HDLc, SBP, and blood glucose (Expert Panel on Detection 2021).

8.4 Changes in body composition and cardiorespiratory fitness

Post-intervention measurements showed that there were significant changes in the body composition. Fat mass, body fat percentage and visceral fat all declined significantly, while body weight also slightly decreased. In addition, skeletal muscle mass significantly increased after six months. On the other hand, maximal oxygen uptake, VO_2max also slightly improved with a mean difference of 1.34 ml/kg/min. This remains consistent with the large body of evidence showing that physical activity alters body composition and improves cardiorespiratory fitness. Subsequently, regular exercise is a powerful tool to mitigate cardiovascular disease risk in already metabolically compromised individuals. Specifically, mechanisms involved in effects of increase in physical activity levels or decreased sedentary times include improved vascular health, improved glucose control, adaptations to central and peripheral vasculature, and cardiac remodelling (Valenzuela P. et al. 2023).

8.5 Limitations

One of the major limitations of the study is the sample size. Eleven participants might be an underestimate when attempting to show significant changes specifically in some important parameters such as blood pressure and lipid profile. While there were almost identical number of male and female participants, the age range is wide. It is well noted that age is a major factor in most of normative values and measurements like arterial stiffness and blood pressure. A priori power calculation requires a minimum of 58 participants to demonstrate at least 10% change in PWV, given that the sample is not severely heterogeneous.

Structure of exercise therapy sessions is another limitation in the study. It was mentioned that ExT was prescribed to the patients, however, there was no clear regimen and dose of exercise. Hence, it was beyond the scope of this study to monitor the amount, volume, and intensity of the exercise programs that the patients underwent. Training intensities and dosage of exercise prescription are essential components in a randomized controlled trial. Also, the lack of a control group prohibits the study to provide comparison on dose-response relationship of ExT to the measured variables and differences between exercise and non-exercise patient groups.

Another limiting factor would be the choice of measurement of arterial stiffness. Arteriograph has a high reliability and very user independent, however, in human patient trials and clinical settings, a different and more accurate type of device would be necessary. The rationale behind the use of the Tensiomed device was that it was easy to use on the patients. Measuring carotid-femoral PWV would require a highly skilled specialist because of some patient factors such as adiposity. In addition, the gold standard, non-invasive diagnostic test in measuring arterial stiffness is cfPWV. In this study, arteriograph was performed on the brachial artery, which might limit or miscalculate PWV values.

9 CONCLUSION

The main objective of the study was to examine changes on vascular function in patients who were diagnosed with cardiometabolic syndrome after six months of exercise therapy. The combined aerobic, resistance, and home exercises as an exercise therapy program prescribed to the patients was successful in inducing positive changes especially on arterial stiffness and body composition. It supports evidence on exercise effects on vascular function in clinical population. The results also showed how blood pressure and blood lipid profile were slightly improved after six months.

Utilization of exercise therapy or physical activity to mitigate increased cardiovascular risk in individuals who are at high risk, ie. hospital patients with non-communicable chronic disease is a major takeaway from this study. The results of this study may help design more organized exercise therapy protocols for clinical population to reap the benefits of exercise, mitigate eventual adverse diseases, and reduce mortality and morbidity.

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