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# Autonomic and Vascular Adaptations to Exercise: Implic ations for Cardiovascular Health

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## ABSTRACT

Exercisers typically experience far less cardiovascular and metabolic disease compared to sedentary individuals. Thus, a sedentary lifestyle contributes to the world-wide high incidence of cardiovascular disease, hypertension, and type 2 diabetes. Degradation of a number of key autonomic cardiovascular markers appears to be consistently associated with the development of these lifestyle diseases. Three important autonomic cardiovascular markers include reduced heart rate variability, reduced baroreflex sensitivity, and increased arterial stiffness. Heart rate variability can be assessed through spectral analysis and baroreflex sensitivity through examination of the rise and fall of heart rate and systolic blood pressure. Elevated arterial stiffness, the stiffening of arteries, can be assessed though the reflected wave and pulse wave velocity. These three markers worsen as aging progresses. High arterial stiffness and reduction in heart rate variability and baroreflex sensitivity, however, can be improved with involvement in exercise. All markers have been found to improve after continuous steady state exercise and/or interval exercise combined with resistance exercise. A number of studies have indicated that both acute and chronic exercise can reduce arterial stiffness and improve heart rate variability and baroreceptor sensitivity in both healthy and hypertensive individuals. Also older individuals who exercise regularly improved their cardiovascular and autonomic function. Thus, incorporating regular exercise into an individuals' lifestyle is important as regular exercise may decrease the incidence of cardiovascular disease, hypertension, and type 2 diabetes by preventing a reduction in heart rate variability and baroreflex sensitivity, and increase in arterial stiffness.

**KEYWORDS**: Heart rate variability; Baroreflex sensitivity; Arterial stiffness; Exercise

# INTRODUCTION

Cardiovascular disease (CVD) is one of the major causes of world-wide morbidity and mortality and according to the American Heart Association [1] is likely to further escalate in the near future. It has been predicted that by 2030, 40% of US adults will have at least one form of CVD that is likely to result in a tripling of the medical health care costs of CVD [1]. The increase of CVD is mainly caused by the aging of populations. Lack of exercise together with a family history of certain diseases also makes a significant contribution to the severity of CVD. Low aerobic fitness has been considered as the major risk factor contributing to morbidity and mortality regardless of body mass index [2]. Although hereditary is one factor that cannot be changed, leading an active lifestyle has the potential to reduce the severity of CVD. Physical activity is so important that failure to lead a physically active lifestyle can result in several abnormalities such as high blood pressure, metabolic syndrome, and type 2 diabetes [1]. Degradation in several key autonomic cardiovascular dysfunction markers have been shown to predict CVD development [1]. These include heart rate variability (HRV), baroreflex sensitivity (BRS), and arterial stiffness. High level of HRV is an indicant of healthy parasympathetic activity and is a marker of the body's ability to respond to cardiovascular perturbation.

HRV and BRS have been found to decline with age. The decline of HRV with age has been considered to be an independent marker of CVD and has been shown to contribute to increased risk of mortality [3] and a reduced parasympathetic activity. Several studies have shown that HRV declines with age by 14% to 23% per decade [4,5]. Some studies examining middle-aged populations [6,7] and elderly men and women [8-10] have found that exercise increases HRV, whereas other studies [11,12] have found no change in HRV with improvement in BRS [11]. BRS has been found to decrease with age [13,14], hypertensive [15] and overweight/obese [16] individuals, and in postmenopausal women [17-20]. Regular exercise, however, has been found to restore BRS function. For example, older individuals who underwent high intensity interval training (HIIT) on a cycle ergometer for 14 weeks not only have improved their BRS, but also improved their maximal oxygen uptake by 19% [21]. The different outcomes of the effects of exercise on HRV and BRS are likely due to differing protocols, participants, and individual differences in the exercise response.

Arterial compliance, and its inverse arterial stiffness, can be defined as the ability of an artery to distend in response to intravascular (transmural) pressure [22]. Arterial stiffness, which is an indicant of the stiffening of the large arteries increases with age, especially in central arteries such as the aorta and carotid artery. Arterial stiffness can be reflected by β stiffness index and Young's elastic modulus [23]. It has been suggested that increases in arterial stiffness is due to a progressive increase in collagen content and elastin in arterial walls [23]. High arterial stiffness has also been found to be associated with metabolic syndrome, and diabetes. Two indices that are commonly used to determine stiffness of the large artery are augmentation index (AIx), which is reflected wave and carotid-femoral pulse wave velocity (PWVcf), which is considered the gold standard of arterial stiffness measurement. It is known that arterial stiffness increases with age and conditions such as hypertension and diabetes mellitus also contribute to the increase in arterial stiffness [24]. It has been suggested that arterial stiffness contributes to the impairment of BRS in older populations and it also appears that arterial stiffness is an independent determinant of impaired BRS [25]. Increased prevalence of arterial stiffness has also been found in overweight and obese individuals [26]. Other studies have also shown that there is association between arterial stiffness and BRS [14,27].

Exercise has been widely used as preventative medicine to reduce the incidence of cardiovascular and metabolic disease related to unhealthy lifestyle. Lack of exercise combined with a sedentary lifestyle contributes to an increase in risk of cardiovascular disease. Types of exercise used in past research are aerobic exercise (continuous walking, jogging, cycling), HIIT and resistance training. Thirty minutes of moderate aerobic exercise, 3 times per week for 4 weeks, has been found to improve aerobic fitness and reduce arterial stiffness, assessed by AIx, in young normotensive males with a family of hypertension [28]. Whereas, another form of exercise, 20 minutes of HIIT performed 3 times per week for 12 weeks also improved HRV and BRS, and reduced AIx in young overweight males [29]. Cross sectional studies using physically active and sedentary individuals have shown that exercise can maintain a healthy arterial system. For example, older endurance trained adults possessed lower arterial stiffness than their sedentary counterparts, suggesting that they had high carotid artery compliance [30]. Also, trained postmenopausal women had lower arterial stiffness compared to sedentary women and similar arterial stiffness to that of trained premenopausal women [31]. It is clear that involvement in regular exercise has the ability to alleviate aberrations in autonomic function and arterial stiffness.

Thus, the purpose of this review is to provide an overview of autonomic and vascular function accompanying the aging process and certain health conditions and also to describe how exercise can play a key role in preventing a decrease in the reduction in autonomic and vascular function. Exercise modalities and possible mechanisms underlying exercise-induced changes in autonomic and vascular function are also described.

## AUTONOMIC FUNCTION AND EXERCISE

The autonomic nervous system plays an important role in controlling blood pressure and heart rate and the development of hypertension. Hypertensive individuals have been shown to possess autonomic dysfunction that is indicated by low HRV and BRS. Both HRV and BRS have been shown to be reduced with aging and hypertension [32]. It has also been well established that autonomic dysfunction is associated with conditions such as overweight, obesity, and diabetes [33,34]. The decline of autonomic function is typically influenced by an accumulation of visceral fat [35]. Lowered autonomic function was also found to be correlated with higher abdominal-to-peripheral body fat distribution measured by Dual energy X-ray Absorptiometry (DEXA) in both young and old healthy men [36]. These results suggest that visceral fat obesity may contribute to a decline in autonomic function. Also, young individuals with high abdominal adiposity seemed to undergo an early decline and a premature aging of autonomic function [35]. Thus, hypertension and high levels of central adiposity has an unfavorable effect on autonomic function, which is reflected by impaired HRV and BRS.

HRV can be defined as beat-to-beat variation in heart rate of individuals in sinus rhythm [37]. Having high HRV is important as HRV is considered to be a marker of autonomic regulation of the heart [38]. Typically, HRV is assessed through two frequency components; high-frequency power (HFP) that reflects efferent parasympathetic activity and is predominant at rest; and low-frequency power (LFP) that reflects sympathetic/parasympathetic interactions and baroreflex activity [39,40]. The LF/HF ratio reflects the relationship between BRS and vagal modulation rather than sympathovagal balance [41]. Low high frequency power and high low frequency power are related to acute myocardial infarction [42] and are involved in triggered sudden death [43]. A reduction of HRV can also be used to identify those who are at high risk of life threatening arrhythmias during acute myocardial ischaemia [39]. A decreased HRV is usually an indication of reduced autonomic regulation of the sino-arterial node [37]. Decreases in parasympathetic activity and increases in sympathetic activity can lead to reduced HRV, resulting in autonomic imbalance [44]. Autonomic imbalance is commonly used as a clinical predictor of low survival in chronic heart failure (CHF) patients [45]. Depressed HRV has also been identified as a cardiovascular risk factor and is correlated with increased mortality risk among patients with and without heart disease [46]. The assessment of HRV as an indicant of autonomic dysfunction has been well established. The information provided by HRV gives an indicator of the autonomic health status in healthy and diseased individuals.

Individuals who regularly incorporate aerobic exercise and physical training into their daily life, such as athletes and sedentary [47] and cardiovascular disease patients [48], have been shown to increase their HRV levels, and an improvement in frequency domain HRV parameters was found following exercise training [49]. Several studies have also shown that improvement in HF and the reduction in LF/HF ratio was found in CHF patients [50-52]. In terms of the duration, frequency, and intensity of exercise needed to enhance HRV, the studies above used moderate aerobic exercise with an exercise intensity between 50% to 80% of heart rate reserve or peak oxygen consumption for 20 to 60 minutes, 2 to 5 times per week, between 8 to 24 weeks [53]. However, HIIT and aerobic training have also been used to induce improvement in HRV in different populations, such as young overweight individuals, type 2 diabetic patients, and older individuals. For example, 20 minutes of HIIT on a cycle ergometer, proceeded with 5 minutes of warm-up and 5 minutes cool-down, 3 times per week, for 12 weeks improved parasympathetic activity [29] in young overweight males (Figure 1).

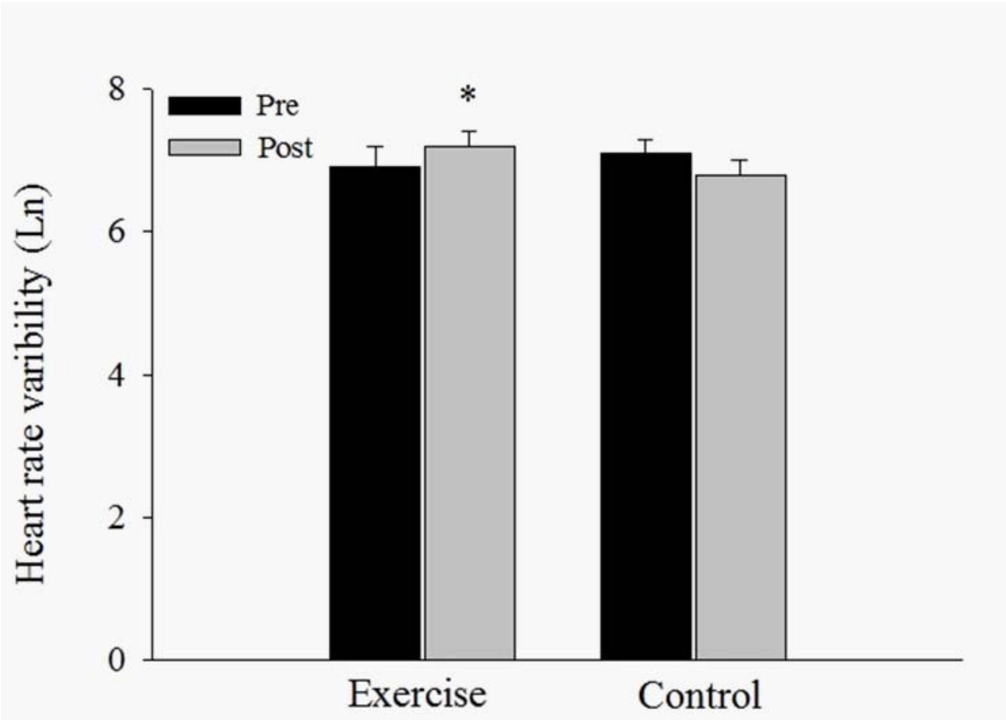


**Figure 1:** Heart rate variability of overweight young males at pre and post 12 weeks of interval sprinting exercise.

A study investigating type 2 diabetic individuals also found similar results when 30 minutes, 4 times per week for 12 weeks of HIIT training on a treadmill resulted in improvement in HRV by 19% [54]. This form of exercise consisted of 3 minutes of warm-up, 6-2 minutes of high-intensity at 80% to 90% of heart rate maximum (HRM), separated by six minutes of moderate intensity at 50% to 60% HRM with 2 minute recovery intervals, and 3 minutes of cool-down. The improvement of HRV in type 2 diabetes is significant as exercise could prevent type 2 diabetic patients progressing to a condition called diabetic neuropathy later in life. Another HIIT study also showed that HRV was improved significantly in older individuals, whose average age was 74 years, following a 14 weeks of cycle ergometer HIIT program [21]. Thus, both steady state continuous exercise and HIIT had positive effects on autonomic function by increasing HRV levels.

Another indicant of autonomic function is BRS. BRS provides information about the ability to increase parasympathetic/vagal activity and to decrease sympathetic activity in response to sudden increase in blood pressure [55] and is also affected by age. BRS is an indicant of how sensitive the body's autonomic nervous system is in responding to sudden blood pressure changes [55]. Low BRS is a marker of reduced compliance of the carotid artery [13,14], which typically occurs with aging. Blunted BRS is also significantly associated with risk of death after myocardial infarction [39,56]. Thirteen weeks of aerobic exercise, however, not only altered cardio vagal BRS, but also increased carotid artery compliance [14], which further suggests that carotid artery compliance plays a key role in age-associated decreased in BRS in healthy sedentary men. Lower BRS has also been found to be associated with high blood pressure, increased sympathetic activity, and disease related to unhealthy lifestyles, such as overweight and obesity. Hypertensive individuals with high abdominal fat have been shown to possess low BRS compared to normotensive individuals [15]. Improvement in cardio vagal BRS was also found in young and old overweight/obese individuals who underwent 3 months of energy restriction that induced 5% to 10% weight loss [57]. A similar study also found that sympathetic activity was declined and BRS was restored in obese individuals following 16 weeks of hypocaloric diet [16]. Another intervention study that employed 12 weeks of HIIT on a stationary bike also found that BRS was improved in young overweight men [29]. Thus, a decline in BRS is associated with age and overweigh/obesity, but incorporating regular exercise and/or hypocaloric diet restored the impairment of BRS in healthy sedentary individuals.

A cross-sectional study with young individual also showed that regular endurance exercisers had higher BRS than that of sedentary individuals [58]. In middle-aged type 2 diabetic men, a combination of aerobic exercise and resistance training twice per week for 12 months resulted in an improvement in BRS by 26% [59]. A study using rabbits with heart failure has shown that treadmill exercise for 30 to 40 minutes per day, 6 days per week for 4 weeks resulted in an improvement in BRS and a reduction in sympathetic activity [60]. A reduction in angiotensin II and angiotensin receptors in the central nervous system may be the underlying mechanisms. Another animal study using spontaneously hypertensive rats also found that following exercise, BRS improved closer to normal values [61]. Authors suggested that increased release of endothelial factors and reduced sympathetic activity play a role in increased BRS [61]. Both human and animal studies have shown that aberrations in BRS can be restored with regular exercise training.

It is well established then, that regular aerobic and HIIT training improves autonomic function, however, the underlying mechanisms are not well understood. Possible explanations could include increases in nitric oxide bioavailability and lower angiotensin II levels [62,63] and reduced sympathetic activity [60]. Another possible contributing factor could be the anti-inflammatory effects of exercise training on autonomic function [64]. Thus, moderate exercise training for 20 to 30 minutes, 3 times/per week, for 12 weeks seems to be sufficient to enhance HRV and BRS even in patients with CHF, which resulted in improvement in autonomic function.

## EXERCISE AND ARTERIAL STIFFNESS: ACUTE AND CHRONIC

Arterial stiffness, which has been considered as an independent predictor of cardiovascular disease, can be assessed through a reflection wave, commonly known as the augmentation index (AIx) and carotid femoral pulse wave velocity (PWVcf), which is considered to be the gold standard of arterial stiffness assessment. AIx, a reflection wave, is commonly assessed by placing an applanation tonometry sensor (SphygmoCor) on either radial artery or carotid artery. AIx then, is derived from the ratio of augmented pressure (AP) and pulse pressure (PP), AP/PP [28]. PWVcf is obtained by dividing the distance from the carotid pulse and femoral pulse as measured by a tape measure by the time taken for the arterial pulse to propagate to the carotid and femoral arteries [65]. Twenty consecutive waveforms are typically recorded to analyse AIx and PWV [28,65]. Another acceptable method to assess arterial stiffness is by assessing ankle-brachial PWV [66]. Thus, arterial stiffness can be assessed using different methods and devices. As long as the methods/devices are in agreement or highly correlated with the gold standard method, derived results should be acceptable and deemed to be valid.

It is known that between the ages of 25 and 75 years, arterial compliance progressively declines by 40% to 50% in healthy sedentary men and women [13]. Aging is accompanied by functional and structural changes in the arterial system. A combination between aging and lack of physical activity can lead to early deterioration of the arteries. The arteries appear to undergo both functional and structural changes, which are due to a decrease in elastin and an increase in collagen [67], which lead to stiffening of the arteries. The susceptibility of both elastin and collagen to non-enzymatic cross-linking, with advanced glycation end products, further stiffens the arterial wall [67]. Functional changes that include changes to vascular endothelial cell and vascular smooth muscle cell can also affect large artery compliance [67-70]. With aging, vascular endothelial function is diminished, nitric oxide bioavailability is decreased, and vasoconstrictor reactivity is altered [71].

The mechanisms underlying the increase in vascular smooth muscle tone is likely an increase in sympathetic nervous system activity and adrenergic receptor stimulation as well as an increase in vasoconstrictor substances, such as endothelin-1 [71]. Compared to sedentary premenopausal women, sedentary postmenopausal women had higher carotid AIx and aortic PWV (central arterial stiffness) and similar peripheral (arm and leg AIx and aortic PWV) arterial stiffness [31]. Physically active postmenopausal women, however, had similar central and peripheral arterial stiffness than that of physically active premenopausal women [31]. Thus, regular aerobic exercise and physically activity seem to inhibit the stiffening of the arteries and are the key to maintaining a healthy arterial system.

Exercise has been widely used as preventive medicine to reduce the severity of conditions or diseases that are related to unhealthy lifestyles. Some studies have shown that aerobic exercise improves carotid artery compliance by 30% in middle-aged men and women [13,72,73]. It has been suggested that aerobic exercise can be used to reverse or de-stiffen the large elastic arteries in older men and women. Also, it has been suggested that the positive effect of exercise on carotid artery compliance in older men who exercise regularly is associated with a consistent maintenance of carotid BRS [14]. Thus, it seems that exercise can positively alter large artery compliance in older individuals.

In young healthy individuals, 30 minutes of acute aerobic cycle exercise significantly reduced arterial stiffness measured by the β-index [74]. Contradictory findings, however, from acute and chronic studies showed that arterial stiffness did not change following acute and 20 weeks of chronic dynamic exercise in older hypertensive men [75]. It is feasible that the aging effect may counteract the positive effect of exercise on arterial stiffness. Arterial stiffness, assessed through AIx, was also reduced by 6% (Figure 2) following 4 weeks of moderate intensity cycle exercise in healthy normotensive young individuals with a family history of hypertension [28]. Longer duration of exercise which involved 12 weeks of aerobic exercise in coronary heart disease patient also showed a decrease in AIx by 4% [76]. Therefore, steady state continuous exercise has also been widely used to induce positive effects on vascular health.

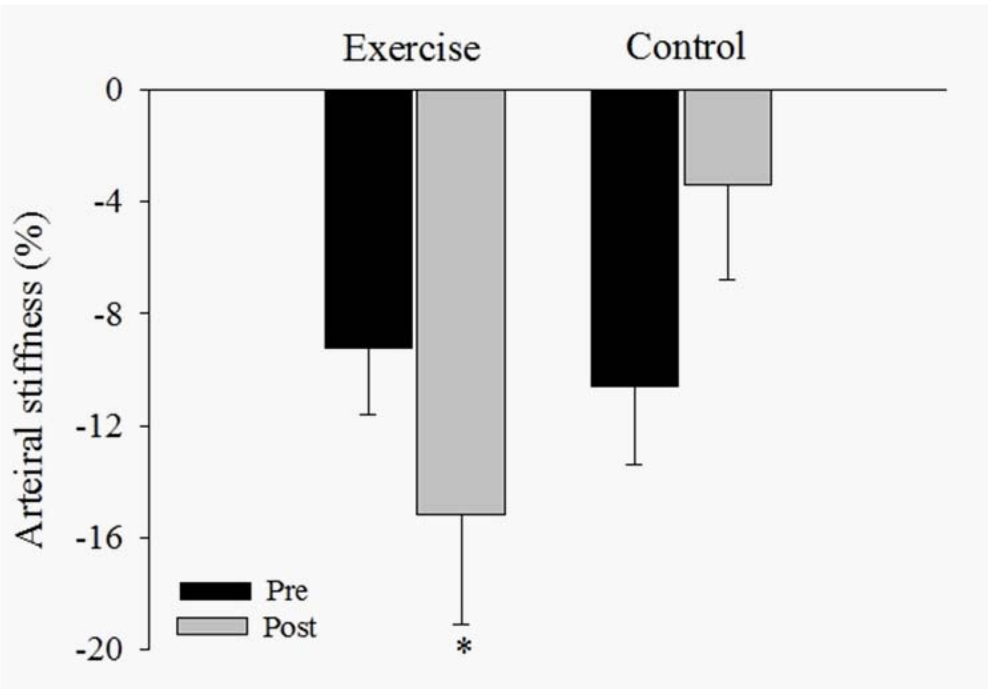


**Figure 2:** Augmentation index of young normotensive offspring of hypertensive parents at pre and post 4 weeks of steady state continuous moderate aerobic exercise.

# EXERCISE MODALITIES

There are a variety of exercises that can be performed to induce positive health benefits. The typical exercise modality that has been recommended is aerobic steady state continuous exercise (SSCT) for at least 30 minutes, 3 to 5 times per week, for a total of 150 minutes per week [77]. The intensity of exercise recommended is usually moderate, which can be determined from a certain percentage of maximal oxygen uptake or maximal heart rate. Another form of exercise that is HIIT has recently emerged and has been widely used to induce health benefits. Modification of interval training protocols, however, may be needed to suit different populations. For example, HIIT to induce athlete performance would be different with the HIIT that would be used to induce cardiovascular health in healthy sedentary or disease individuals. Certain exercise effects or adaptations that occur following HIIT training may not occur or be apparent after SSCT. Depending on the health markers and conditions examined, the magnitude of change following SSCT may be smaller than that of HIIT. For example, arterial stiffness, assessed through PWV [78-80] and autonomic function [80] are normalized following HIIT in hypertensive individuals, but not following continuous moderate exercise. With HIIT training, the exercise compliance rate was found to be less [29,81] compared to SSCT. HIIT is also deemed to be superior in terms of improvement in cardiovascular health compared to SSCT [78]. Thus, HIIT may be needed to be incorporated into daily life to induce health benefits.

HIIT defined as repeated bouts of high intensity exercise interspersed by rest for 20 to 30 minutes has also been used to prevent or to reduce severity of diseases related to unhealthy lifestyles. HIIT has been found to improve cardiac and metabolic health of young overweight males [29] and females [81]. The AIx was found to be reduced by 4% (Figure 3), whereas PWVcf velocity was also reduced by $0.4 m \cdot sec^{-1}$ (Figure 4) following 12 weeks of HIIT in young overweight males [29]. The HIIT employed was an 8-sec pedaling sprint at a cadence of 100 to 120 revolutions per minute (rpm) at 0.5 to 1 kg of load, followed by a period of lighter intensity exercise at a cadence of 30 to 40 rpm for 12 seconds, repeated for 20 minutes. Another type of HIIT included cycling on a bike at 80% to 85% of maximal oxygen uptake ($VO_2$ max) for 4 minutes with 5-minute rest intervals, repeated 6 to 8 times [82]. The HIIT has been used in a number of clinical groups involving cardiac rehabilitation, chronic obstructive pulmonary disease, and intermittent claudication disease patients. Thus, varieties of interval training have been employed to improve cardiovascular and metabolic health.

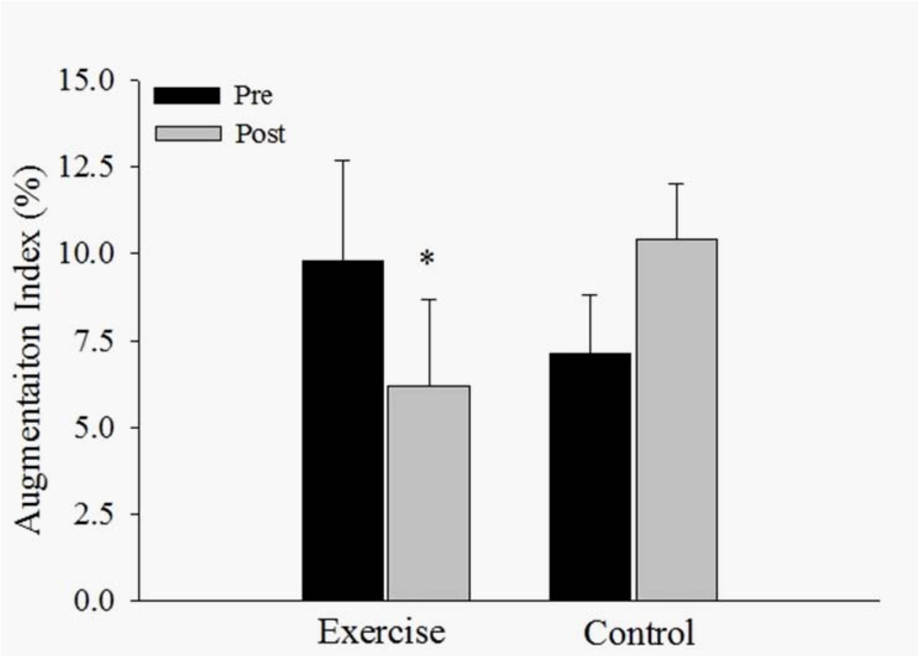


**Figure 3:** Augmentation index of young overweight males at pre and post 12 weeks of interval sprinting exercise.

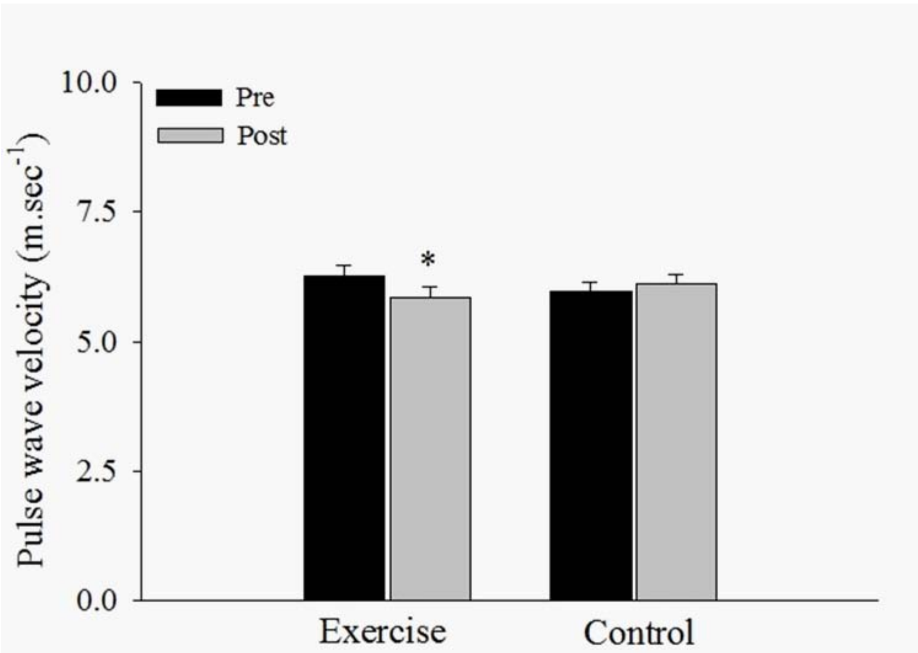


**Figure 4:** Pulse wave velocity of young overweight males at pre and post 12 weeks of interval sprinting exercise.

Participating in resistance exercise is important to maintain muscle mass that declines with in aging. The effect of resistance training on arterial stiffness, however, is equivocal. Several studies [83,84] have shown an unfavorable effect of resistance training on arterial stiffness, whereas others have shown no alteration in arterial stiffness [85,86]. A meta-analysis [87] showed that young adults had their arterial stiffness elevated from 14.3% to 20.1% following high-intensity resistance training. In contrast, it has been shown that progressive high-intensity resistance training without an increase in training volume did not alter arterial stiffness in young individuals [86]. Interestingly, the association between resistance training and arterial stiffness was not found in middle-aged individuals [86]. Although high-intensity resistance training has been found to increase arterial stiffness by 11.6%, moderate intensity resistance training did not seem to induce the same effect [86]. Another study showed an unexpected finding that improvement in muscular strength in young individuals was inversely correlated with arterial stiffness [88]. This finding suggests that resistance training attenuates arterial stiffness. Different protocols and populations possibly contribute to variability of results. Further studies looking at resistance training and arterial stiffness need to be carried out.

# CONCLUSIONS

Autonomic dysfunction is associated with age, hypertension, overweight, obesity, and type 2 diabetes and is considered to be a predictor of cardiovascular disease and mortality. Aberration in autonomic function, commonly expressed as impairment in HRV and BRS can, however, be restored back to its normal value through regular exercise participation. Impaired arterial stiffness, typically known as high AIx and PWVcf, is another dysfunction that is also associated with age and the aforementioned health conditions. Acute and chronic exercise has been used to induce reductions in arterial stiffness in both young and older individuals. The mechanisms underlying improvement in autonomic function and arterial stiffness are not well understood. However, reduced sympathetic activity, increased endothelial derived relaxing factors, and increased large artery compliance are postulated to explain exercise-induced improvement in autonomic function and arterial stiffness. In terms of the type of exercise, both aerobic exercise and interval sprinting exercise exerted health benefits, however, interval sprinting training has been found to be superior in inducing cardio protective benefits in healthy sedentary and diseased individuals. The intensity of the interval training can also be modified to suit the fitness level of the participants. Overall, autonomic and vascular function is altered with age and with certain health states. Incorporating regular exercise in the form of interval sprint training combined with resistance training, to induce and to restore autonomic and vascular function is highly recommended.

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