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Regular Physical Activity and Vascular Aging

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Abstract: Background: Aging and low physical activity are associated with the development of diseases (hypertension, type 2 diabetes, dyslipidemia, obesity) marked by chronic low-grade inflammation. Cardiovascular disease is the most common cause of death worldwide, while exercising muscle tissue can increase the secretion of myokines that can reestablish a possible inflammatory process in virtue of the anti-inflammatory effect. Methods: The objective of this review is to focus on molecular mechanisms involved between different kinds of exercise and cellular oxidative stress, and the emerging therapeutic strategies which have the potential to promote benefits in vascular health. Results: Regular exercise increases shear stress, mitochondrial biogenesis, and upregulates mitochondrial antioxidant system, inducing anti-inflammatory actions, such as suppression of TNF-α which may offer protection against TNF-α-induced vascular impairment. Conclusion: Exercise training of various durations and intensities appears to prevent and restore the age-related impairment of endothelial function, likely through the restoration of NO availability, reduction in oxidative stress, and turnover of the apoptotic process in the endothelium, thus minimizing vascular inflammation and decreasing the formation of atherosclerotic plaques.

Keywords: Oxidative stress, endothelial dysfunction, atherosclerosis, exercise, physical activity.

1. INTRODUCTION

1.1. Human Aging: Effects on the Cardiovascular System

Between 2000 and 2050 the elderly population, defined as 60 years of age or older, will reach a number of 2 billion according to the World Health Organization (WHO) [1]. The process of aging is associated with changes in body composition [2, 3] which lead to significant compromises in components of physical fitness [4] and individual health favoring, directly or indirectly, the development and progression of diseases such as type 2 diabetes, hypertension, dyslipidemia and cardiovascular diseases (CVD) [5]. In the elderly, cardiovascular aging is a determinant factor of life span [6] and major reductions in capacity and function observed in aging are associated with physical disability [7] and higher incidences of chronic diseases to such an extent that CVD is responsible for one third of deaths worldwide [8].

Several alterations occur in the cardiovascular system during aging that can be subdivided in morphologic and metabolic changes, and thus, it is clear that the impairment of this "machine" is multifocal given that conformational modifications directly affect system functionality [9, 10]. Many of these changes occur within the heart, as heart weight increases due to left ventricle hypertrophy and cardiomyocytes proliferation [11, 12], and consequently diastolic parameters and cardiac output are altered. In the vascular system arterial stiffness increases and thickening of arterial intima and media layers occur, especially in the aorta [6]. Additionally, the migration and proliferation of vascular smooth muscle cells directly influence blood pressure and increase hypertension prevalence [13].

In general, the impairment of endothelial vasodilation is one of the manifestations of arterial aging preceding vascular dysfunction associated with CVD [14]. One of the many alterations found in cardiovascular aging and associated with the aging process and CVD that is a major risk factor for cardiovascular morbidity and mortality is vascular calcification [15]. Vascular calcification is characterized by a degenerative pathology of the vessel wall via thickening and elasticity loss due to atherosclerotic plaque or mineral deposition, which may be present in distinct forms such as intimal calcification, medial calcification, and may also be found in the artio-ventricular valves of the heart [16]. Because the calcification process is associated with arterial thickness and stiffness the main consequence is an abnormal arterial pressure/flow wave, leading to an increase in systolic pressure and decrease in diastolic pressure and ultimately resulting in high blood pressure [17]. Calcification of semilunar valves causes an abnormal narrowing of the arterial lumen, termed stenosis, that results in significant changes in mechanical properties of the heart due to changes in morphology and function (i.e. aortic valve surface area and smaller valve openings) [18] leading to an increased risk of cardiac events and mortality [19].

1.2. Cardiovascular Aging: The Immunometabolic Profile

In addition to the morphological changes that occur in the heart and large vessels described in the previous section, significant immunological, endothelial and metabolic alterations occur throughout the body and reflect systemic modifications.

In 1956 Denham Harman proposed one of the most accepted theories in vascular aging whereby morphological changes directly influence metabolism, relating the process of vascular aging with the production of free radicals or reactive oxygen species (ROS) [20]. Currently it is known that unbalanced concentrations of ROS interfere with the nitric oxide (NO) signaling pathway evidenced by higher ROS concentrations decreasing NO bioavailability [21] which may directly influence vascular aging by promoting vascular
dysfunction, pathology, and inflammation [22]. In this context, a cohort study with 88 subjects aged between 56.6-59.7 years old of both genders reported that NO concentrations are higher in subjects with longer relative telomere length. The concentration/activity of other plasma oxidative stress biomarkers, such as protein carbonyl, F2-isoprostanes urinary, superoxide dismutase and glutathione peroxidase, are also lower in subjects with longer relative telomere lengths. This suggests that endothelial dysfunction, associated with high levels of oxidative stress could lead to incremental telomere attrition [23], and that NO bioavailability could influence longevity given that telomeres are considered “raffinate biological clocks”.

During the aging process there is a reduction in NO concentrations and concomitant increase in oxidative stress with higher ROS synthesis and release. Several mechanisms and/or enzymes can generate ROS, such as xanthine oxidase, uncoupled NO synthase, the mitochondrial respiratory chain and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. NADPH oxidase is one of the major enzymes responsible for superoxide anion synthesis, which in turn reacts with NO to produce peroxynitrite which promotes endothelial nitric oxide synthase (eNOS) uncoupling and contributes to increased ROS and reduced NO [24]. In a recent review about arterial modifications and their impact on metabolism and the inflammatory profile Antunes et al. [25] elucidated the control mechanism of NO on endothelial function. In addition to injury and tissue modifications leading to an imbalance between NO and ROS, there is also the activation of several inflammatory pathways mediated by a nuclear transcriptional factor kappa B (NF-kB) that enables gene transcription of inflammatory factors such as interleukins (IL-6, -1β), chemokines (MCP-1) and tumor necrosis factor alpha (TNF-α).

Besides directly modulating the activity of immune cells, the synthesis and secretion of immunomodulatory proteins can also increase endothelial dysfunction. In particular, Moreau et al. [26] suggest that TNF-α contributes to impaired endothelial-dependent vasodilation and arterial stiffening in estrogen-deficient postmenopausal women. Another pro-inflammatory cytokine associated with aging and CVD development is macrophage migration inhibitory factor (MIF) [27] which is an atherosclerosis risk factor linked with arteral stiffness and vascular aging. In this perspective Rammes et al. [28] investigated nutritional strategies to reduce MIF concentrations in elderly and reported that nitrate supplementation for 4 weeks (sodium nitrate 150 μmol/kg body weight) decreased plasma MIF concentrations and improved vascular function via a reduction in central systolic blood pressure. In a pioneer nutritional observational study, Gardener et al. [29] observed that Mediterraneaen style diet adherence was inversely associated with plaque thickness and median plaque area even when the results were adjusted for vascular disease biomarkers such as HDL-c and triacylglycerol concentrations, as well as anti-hypertensive, cholesterol-lowering and diabetes medications, BMI, and previous cardiovascular disease.

Therefore it is worth emphasizing that diet related behavior modifications may prevent, delay, and/or treat the effects of vascular aging. Additionally, diet related modifications may assist directly in controlling highly prevalent diseases in the elderly such as dyslipidemia, hyperglycemia, and hypertension, which are significantly associated with endothelial dysfunction. In an observational cohort study with older adults (4,707 participants mean age 75 years), Miedema et al. [30] verified that free fatty acids were significantly associated in a concentration-dependent manner with higher total mortality and cause-specific mortality such as cardiovascular disease. It is important to highlight that higher free fatty acid concentrations, especially LDL-c type, are more susceptible to interact with ROS resulting in molecules of oxidized LDL. LDL_{ox} can generate toxic injury to the endothelial wall leading to atheroma plaque formation and adhesion, endothelial dysfunction, and consequently, the initiation of an inflammatory profile via cytokine production and immune cell recruitment [25]. On the other hand, van Schalkwijk et al. [31] calculated lipoprotein metabolism indicators for 1,981 subjects and reported that VLDL was more associated with increased cardiovascular risk compared to LDL. A longitudinal follow-up study (9.4 years) verified that increased aortic stiffness is implicated in the age-associated increase in systolic blood pressure and pulse pressure, and this data suggests that arterial wall stiffness, according to age and sex, modulates the blood pressure trajectories during aging in men [32].

Chronological aging is a universal process that affects each and every living organism. Biological aging, however, may be attenuated through behavioral changes that include but are not limited to dietary modifications, stress and quality of life modifications, and regular physical exercise. These topics will be discussed in greater depth in the following sections.

2. EXERCISE AND VASCULAR AGING

Aging and low physical activity are associated with the development of diseases such as hypertension, type 2 diabetes, dyslipidemia, obesity, and metabolic syndrome that are marked by or exacerbate chronic low-grade inflammation [33] and increase the risk of cardiovascular disease [34]. On the other hand, contracting muscle tissue can increase the secretion of anti-inflammatory myokines (IL-1ra, IL-6, IL-7, IL-8, IL-10, IL-15, IL-18, LIF) which suppresses NF-kB, and may thereby reestablish a lower level of systemic inflammation with consistent exercise [35, 36].

The endothelium plays an important role in modulating vascular function by releasing NO which inhibits platelet adhesion and decreases vascular resistance and smooth muscle cell proliferation [37]. Furthermore, endothelial cells are the primary site of the synthesis and release of tissue-type plasminogen activator (t-PA) which prevents fibrinolysis and thrombosis. Our group demonstrated that sedentary subjects have higher plasminogen activator inhibitor-1 (PAI-1) and lipoprotein levels than highly trained athletes [38]. In addition, we found that consistent high intensity and high volume exercise may reduce cardiovascular risk.

The adaptations to exercise that benefit vascular aging vary according to age and gender. As such, practitioners and researchers will manipulate variables such as mode, duration, volume, intensity, frequency and the recovery interval to optimize adaptation in part by altering the immunometabolic response to training.

2.1. Aerobic Training

It is well documented in the literature that regular physical exercise and dietary modifications are efficient strategies to reduce risk factors associated with coronary artery disease, hypertension, type 2 diabetes, obesity, dyslipidemia and endothelial dysfunction [39, 40]. Physical exercise promotes anti-inflammatory and anti-atherogenic responses [41] that may be partially attributed to the reduction in disease risk.

Several endothelial proteins associated with cardiovascular aging and vascular stiffness are affected by aerobic exercise such as endothelin-1 (ET-1). ET-1 induces vasoconstriction and vascular smooth muscle cell proliferation, increases vascular tone, and has been associated with the progression of several chronic diseases such as hypertension, type 2 diabetes and atherosclerosis [42]. It is important to highlight that the conversion of inactive pro-ET-1 to the active ET-1 may be enhanced by the catalytic action of matrix metalloprotease type 2 (MMP-2). This conversion leads to increased blood pressure and augments inflammation via the transcription factor v-ets erythroblastosis virus E26 oncogene homolog 1 (Ets-1) [43]. Aerobic exercise, however, is able to regulate the matrix metalloprotease in skeletal muscle of healthy adults and patients with type 2 diabetes [44]. Thus, endothelial changes mediated by ET-1 may be modified by exercise [42].
A positive correlation between ET-1 plasma concentrations and age has been reported as concentrations of ET-1 significantly increased with age (1.02 +/- 0.08, 1.33 +/- 0.11, and 2.90 +/- 0.20 pg/ml in young (aged 21-28), middle-aged (aged 31-47), and older women (aged 61-69), respectively) regardless of health status [45]. Maeda et al. [45] demonstrated that three months of aerobic exercise training (cycling on a leg ergometer at 80% of ventilatory threshold for 30 minutes per day, 5 days per week) resulted in decreases in plasma concentrations of ET-1, and consequently, a reduction in blood pressure in older women. These results further demonstrate that aerobic training is an effective means to prevent or to treat the progression of hypertension or atherosclerosis and suggest that reductions in ET-1 concentrations and may play a role in these benefits.

Years later the same group observed that 12 weeks of aerobic training (cycling on a leg ergometer at 80% ventilatory threshold for 30 minutes per day for 5 days per week) also promoted modifications in other important biomarkers that are diminished with the aging process, such as NO bioavailability. Maeda et al. [46] observed in fifteen untrained older women (aged 59-69), divided in two groups (exercise group n=10; mean age, 63+4 years and sedentary control group: n=5; mean age, 64+4 years), a reduction in blood pressure at rest after three months of training in the exercise group. Plasma concentrations of NOx (the stable end product of NO by nitrite/nitrate) and cGMP (cyclic guanosine monophosphate, a second messenger of NO) significantly increased only in the aerobic training group, suggesting that the antihypertensive and anti-atherogenic effects of aerobic exercise are also mediated by increasing available NO.

One possible mechanism by which exercise reduces NO inactivation is its relationship with ROS. When ROS are present, NO is degraded to peroxynitrite, however, exercise leads to ROS detoxification by inducing superoxide dismutase activity and NO is degraded to peroxynitrite, however, exercise leads to ROS inactivation is its relationship with ROS. When ROS are present, NO bioavailability may be compromised in the arterial circulation by promoting higher eNOS expression and increased oxidative stress; however, lifelong physical activity reduces concentrations of NOx in both older groups whereas in young group the infusion did not affect the NOx concentrations. In addition, skeletal muscle protein concentrations of endothelial and neuronal NO synthase were higher in these older groups. On the other hand, when the subjects performed 10 minutes of knee-extensor exercise, first with an absolute workload of 12 watts and next with a relative workload corresponding to 45% of the maximal workload (45% Wmax), Nyberg et al. [47] reported lower leg blood flow response associated with a lower leg oxygen uptake in the older sedentary group suggesting that the improved bioavailability of NO by NAC did not increase blood flow during exercise. NO bioavailability may be compromised in the systemic circulation and in the musculature of sedentary aging humans due to increased oxidative stress. However, lifelong physical activity opposes this effect within the trained musculature and in the arterial circulation by promoting higher eNOS expression and NO bioavailability in virtue of an elevated response to the endothelium-dependent vasodilator acetylcholine (ACh). Improvements in ACh can also be observed when combining aerobic exercise with dietary modifications in high-risk groups, and stronger improvements in ACh in the microcirculation have been associated with improved cardiorespiratory performance at the ventilatory threshold [49].

Meilhac et al. [50] investigated the effects of oxidation on NO with 32 male C57BL/6 / 64 LDLr−/− mice trained on a treadmill for 12 weeks (30 minutes at 15 m/minute by 5 days per week) supplemented with or without a synthetic antioxidant (vitamin-E supplement with approximately 0.5 IU of α-tocopherol). Aerobic exercise was found to provide antioxidant protection in the arterial wall via an increase in antibodies to oxidatively modified proteins, such as catalase and eNOS. Conversely, supplementation with vitamin-E during exercise training was found to be deleterious by inhibiting antioxidant enzymes in the arterial wall. This suggests that the adaptations to exercise may provide more oxidative protection than supplemental anti-oxidants such as α-tocopherol and ascorbic acid.

Asymmetric dimethylarginine (ADMA), an inhibitory protein of nitric oxide synthase that is elevated with advancing age and menopausal status, promotes endothelial dysfunction and arterial stiffness [51]. Tanahashi et al. [52] investigated the effects of 12 weeks of progressive aerobic exercise (2-3 sessions per week initially with 30 minutes per day at 60% of maximal heart rate progressing to 40-60 minutes per day at intensity of 65%-80% of maximal heart rate) on AMDA in thirty postmenopausal women. Aerobic exercise training significantly increased carotid arterial compliance and decreased ADMA concentrations. Additionally, changes in carotid arterial compliance were inversely correlated with changes in plasma ADMA concentrations.

Although the effects of moderate intensity continuous exercise have been extensively studied, high intensity interval training is emerging as another potential treatment with beneficial effects on vascular aging. High intensity interval training involves performing short periods (15 to 1 min) of very high intensity exercise followed by a similar period of active recovery. Most high intensity interval training programs are performed on cycloergometers or treadmills with the ability to control for cadence/power output and speed, respectively.

High intensity interval training has been shown to enhance the anti-inflammatory [53] and metabolic responses (i.e. insulin sensitivity, blood lipids profile) and improves body composition effects [54]. Fallahi et al. [55] investigated the effects of eight weeks of high-intensity interval training (4 minutes at 80-100% VO2max and 3 minutes at 50-60% VO2max) on NO metabolites (NO2−, NO3−) and myocardial infarct size after Ischemia/Reperfusion injury in healthy male mice and observed a significant increase in nitrite (34.79%), nitrate, (149.48%) and NOx (98.11%) and smaller myocardial infarct size (23.2%) compared to controls.

In humans, Vezzoli et al. [56] analyzed the effects of 8 weeks of high-intensity interval compared to moderate intensity continuous training on oxidative damage in twenty long-distance masters runners (aged 47.8 ± 7.8) equally divided in two groups: continuous moderate-intensity training (three different types of training sessions were scheduled three days/per week: i) 64-5 minutes at 70% gas exchange threshold (GET); ii) 58.5 minutes at 80% GET and iii) 54 minutes at 90% GET), and high-intensity interval training (three different types of training sessions were scheduled to three days/per week: i) 18x (1 minute at 120% GET, 2 minutes at 65%); ii) 18x (1 minute at 130% GET, 2 minutes at 65%) and 18x (1 minute at 140% GET, 2 minutes at 65%). Both training protocols decreased concentrations of oxidative damage markers such as thiobarbituric acid reactive substance (TBARS), total antioxidant capacity and 8-hydroxy-2-deoxyguanosine (8-OH-dG), however, there were no differences between groups. This data suggests that high-intensity interval training does not cause a higher level of exercise-induced oxidative stress compared to continuous moderate-intensity training, and provides a lower duration alternative to moderate-intensity continuous training with similar anti-oxidant benefits.

It has been postulated that elderly sedentary adults may not be able to tolerate the higher frequency (≥ 3 days/week) of high intensity interval training often prescribed. Grace et al. [57] investigated the effectiveness of lower frequency high intensity interval training (training sessions occurred every 5th day consisting of 6 sprints of 30 seconds at 50% of peak power output) following 6
weeks of basic conditioning on vascular function of lifelong sedentary men (62.7 ± 5.2 years) and compared the effects to lifelong exercisers (61.1 ± 5.4 years). After 6 weeks of basic conditioning exercise (walking, walk/jogging, jogging, cycling, (flat terrain) cycling, (hill terrain) at 55-65% heart rate reserve) the sedentary group improved flow mediated dilatation, however, 6 weeks of lower frequency high intensity interval training failed to further improve flow mediated dilatation. Flow mediated dilatation remained unaffected by lower frequency HIIT in lifelong exercisers suggesting that this high intensity interval training model is effective at maintaining improvements in vascular function achieved during conditioning exercise but does provide enough stimulus to further improve vascular function in physical active older men.

Dall et al. [58] investigated the effects of 12 weeks of high intensity interval training with cycloergometers (3 times per week lasting 30 minutes/session, with a total of 16 minutes of interval training with alternating intervals of 4-, 2- and 1-minute duration at >80% of VO2peak) compared with continuous moderate intensity training (biking for 45 minutes with an intensity corresponding to 60% to 70% of VO2peak) on oxygen uptake, vascular function and psychological distress in sixteen heart transplant recipients (mean age= 52 years). High intensity interval training was shown to increase VO2peak and improve health-related quality of life measured via the 36-item short form, however, endothelial function was not improved. In general terms, high-intensity exercise can promote beneficial adaptations on the cardiovascular system in healthy adults (Fig. 1), however the application alone or combinations that use high intensity interval training require further research to elucidate the most effective prescription in older and diseased populations.

Regular exercise has been associated with a chronic anti-inflammatory response, decreased C-reactive protein (CRP) and vascular adhesion molecules, oxidative stress and NF-kB activation [59] and reduced toll-like receptor 4 (TLR4) signaling, which may explain the chronic anti-inflammatory benefits of exercise [60]. Radom-Aizik et al. [61] investigated high-intensity interval training (HIIT= 10 bouts of 2 minutes with 1 minute of rest interval between sprints) in healthy young men and observed a downregulation of monocyte TNF, TLR4, and CD36 genes. Additionally, high intensity interval training induced a novel genomic profile on circulating monocytes that marked improved vascular health. In this context, Lesniewski et al. [62] demonstrated the anti-inflammatory effects of aerobic exercise on aging arteries. Young and old mice performed 10-14 weeks of moderate-intensity continuous aerobic exercise and a normalization of IKK-NF-kB activation, proinflammatory cytokines, and adventitial-perivascular macrophage infiltration was observed. Miyaki et al. [63] investigated the effects of eight weeks of moderate-intensity continuous aerobic exercise consisting of 30-45 minutes per session and 3-5 days/week on the anti-inflammatory protein pentraxin 3 (PTX3), blood chemistry, and arterial dispensability in postmenopausal women and concluded that PTX3 concentration, high-density lipoprotein cholesterol, peak oxygen uptake, and arterial distensibility increased after the intervention.

In addition to immunometabolic and endothelial changes, interval and aerobic exercise also leads to vascular remodeling and, consequently, improvements in vascular endothelial function occur [64]. Charles et al. [65] conducted a 14-week study in which the lower-limbs were endurance trained on a cycloergometer (10 minutes warm-up; three sequences of 4 minutes at intermediate intensity (70-80% maximal heart rate) followed by 1 minute at high intensity (85-95 % maximal heart rate) followed by 2 minutes of active recovery) in healthy older adults (74±4 years). High intensity aerobic interval training increased aerobic capacity by 11% in the lower limbs, increased citrate synthase activity by 28%, and also caused an increase in the microvascular filtration capacity and...
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microvascularization via an increase in capillary density. This data suggests that aerobic-based interval training is an appropriate physiotherapy to reduce the risk of cardiovascular disease in healthy older adults.

Kitzman et al. [66] conducted a study with sixty-three post-infarct older adults with preserved ejection fraction (70 ± 7 years) in order to investigate the effects of 16 weeks of endurance exercise training (three times per week performing 60 minutes of endurance exercise initially at 40-50% of heart rate reserve for 5-10 minutes, with the intensity increased gradually until 70% heart rate reserve) on endothelial-dependent flow-mediated arterial dilation and carotid artery stiffness. In this specific population there was an increase in VO\textsubscript{2peak} and quality of life, but brachial artery flow-mediated arterial dilation, resting left ventricular systolic and diastolic function and carotid arterial distensability were unchanged. Conversely, Suboc et al. [67] prescribed 10,000 steps per day of physical exercise by pedometers in 114 sedentary older adults (aged ≥50) during to 12 weeks and observed that intervention the group improved brachial flow-mediated dilation. The authors reported that a minimal exercise time ≥20 minutes/day of moderate intensity physical activity was able to enhance flow-mediated dilation, suggesting that even modest amounts of moderate intensity exercise reverses age-related endothelial dysfunction. However, further research with different populations (healthy or at risk populations) is required to further verify these recommendations.

An interesting study recently published by Tarumi et al. [68] demonstrated that diastolic cerebral blood flow velocity and total cerebral blood flow decrease with advancing age while systolic and pulsatile relative amplitude of cerebral blood flow velocity increase. In addition, there are specificities according to sex whereby women showed greater cerebral blood flow and lower cerebrovascular resistance than men. On the other hand, in older population a higher pulsatility of cerebral blood flow was associated with a greater total volume of white-matter hyper intensity thus indicating that central arterial aging has an important role in age-related differences in cerebral hemodynamics.

In conclusion, aerobic exercise of varying intensities, modes, and durations all promote anti-inflammatory adaptations and positively modulate vascular function during the aging process, and require that the health care professional appropriately adapt and prescribe volume, frequency, and intensity according to population to ensure positive adaptation (Table 1).

3. STRENGTH TRAINING

Strength training (ST) has been extensively studied in the literature with the main objective to enhance strength and skeletal muscle hypertrophy [69]. Additionally, ST has been shown to enhance insulin sensitivity and improve glucose tolerance, hypertension, dyslipidemia, and decrease total and abdominal obesity thus minimizing the effect of metabolic syndrome [70], reducing central arterial compliance [71] and consequently also lowering the cardiovascular risk. Miyachi et al. [72] compared young (20-34 years) and middle-age (35-65 years) sedentary or resistance trained males and observed that middle-aged resistance trained men had higher basal whole leg blood flow than the sedentary men, showing that ST may favorably influence leg perfusion during human aging.

Gonzales et al. [73] investigated if age or sex differences are present in common femoral artery (CFA) shear rates during single-leg knee extensor exercise and concluded that older adults (60-79 yr) had overall lower shear rates compared to young adults (20-30 yr) and men had lower shear rates than women. On the other hand, Anton et al. [74] investigated the effects of 13 weeks of ST (1 set to concentric failure with 12 repetitions, about 75% of 1RM, 2 min intervals recovery, 3 times per week) in sedentary men and women (mean age 52 yr) and observed that ST increased basal femoral blood flow and vascular conductance but did not affect brachial blood pressure, plasma endothelin-1 or angiotensin II levels. In animal models, however, Park et al. [75] compared four groups of male Fischer mice divided into young sedentary (4 mo), old sedentary (24 mo), young trained, and old trained and demonstrated that although aging increases angiotensin-induced vasoconstriction, which may be related to the proinflammatory state, exercise decreases the vasoconstriction response.

In relation to the type of stimulus, Dobrosielski et al. [76] investigated the effects of a unilateral handgrip training protocol (nondominant arm, 60% of maximal voluntary handgrip strength, 4 day/week, 20 min per session, and a cadence of 1 contraction per 4 seconds during 1 month) on brachial artery reactivity in 73 to 90 year old men. Unilateral training increased brachial artery reactivity by 45% in the exercise group. Poelkens et al. [77] evaluated the effect of 10 weeks of unilateral arm and leg resistance training on carotid, brachial, and femoral arterial compliance in elderly men with a mean age of 71 years and despite that strength training decreased resting heart rate and glucose, and increased carotid artery peak blood flow, there were no significant changes in peripheral and central arterial compliance.

Ogawa et al. [78] performed a longitudinal study and analyzed the effect of 12 weeks of ST (1 set of 10 repetitions was performed for the foot press, front traction, and shoulder press; 2 series of 10 repetitions were performed for vertical traction using elastic cables, 30 minutes per day and intensity was increased according to requests by subjects) in women with an average age of 85 years and observed improved muscle thickness, CRP, serum amyloid A and HSP70. de Jong et al. [79] investigated the benefits of ST (1 set of 10 repetitions with 60 seconds of recovery intervals and 8 exercises) on coagulation and fibrinolytic responses in patients with coronary artery disease and reported increases in t-PA and decreased PAI-1 immediately post exercise. Furthermore, the reduction in PAI-1 persisted at 1 hour post exercise, showing that strength training seems to positively modulate the fibrinolysis system through increase t-PA concentrations and decrease PAI-1 concentrations.

Queiroz et al. [80] evaluated the effect of ST (3 sets of 8-12 RM, 2-3 min of resting intervals between sets, 9 exercises) on older men and women between 60-74 years of age and concluded that heart rate and rate-pressure product were maintained elevated for up to 4.5 h post-training. Rodrigues et al. [81] analyzed too the effect of a single bout of ST (3 sets of 10 repetitions and 8 exercises) on systolic and diastolic blood pressure, heart rate and rate-pressure product in patients with peripheral artery disease and concluded that a single bout of ST improved blood pressure and cardiac work for one hour after training.

In a longitudinal study, Rossow et al. [82] verified the effects of 8 weeks of high-intensity ST (3 sets, 8-10 repetitions, 80% of 1RM, 60 s of rest between sets, 3 times/week) in young (aged 18-25) and older (aged 50-64) women and concluded that intense ST improved forearm microvascular function but did not affect carotid-femoral or femoral-tibialis posterior arterial stiffness. Panton et al. [83] analyzed 12 weeks of strength training (3 sets of 8-12 repetitions, 60-80% 1 RM, 3 times/week, using 10 different exercises) and observed increases in muscle strength and size but without statistically significant differences for cardiovascular responses to submaximal lower body negative pressure.

Resistance exercise induces angiogenesis and reduces atherosclerosis leading to a greater capillary density and volume within the myocardium and skeletal muscle. Repeated bouts of exercise can induce a significant increase in vascular endothelial growth factor (VEGF) mRNA in human skeletal muscle resulting in an increased number of capillaries per muscle fiber, which enhances O2 transport conductance between microcirculation and mitochondria [84]. The change in acetylcholine-induced vasodilatation is related to shear stress-induced/Akt-dependent phosphorylation of endothelial NO synthase (eNOS) at Serine-1177, and thus exercise may restore
Table 1. Aerobic training-induced alterations on markers related to vascular aging.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Sample</th>
<th>Exercise protocol</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fallahi et al. (2015) (79)</td>
<td>Healthy male mice (N=44)</td>
<td>High-intensity interval training (4 minutes at 80-100% VO\textsubscript{max} and 3 minutes at 50-60% VO\textsubscript{max} during 8 weeks)</td>
<td>↑ nitrate ↑ nitrite ↑ NO\textsubscript{x} ↓ myocardial infarct size</td>
</tr>
<tr>
<td>Dall et al. (2015) (93)</td>
<td>Heart transplant recipients (N=16)</td>
<td>High-intensity interval training in ergometer bikes (3x /week; 30 minutes/session (16 minutes), 4-, 2- and 1-minute duration at &gt;80% of VO\textsubscript{peak}, each separated by a 2-minute active rest period (approximately 60% of VO\textsubscript{peak}) during 12 weeks</td>
<td>↑ VO\textsubscript{peak} ↔ endothelial function</td>
</tr>
<tr>
<td>Scheede-Bergdahl et al. (2014) (71)</td>
<td>Subjects with type 2 diabetes (N=12) and control group (N=9)</td>
<td>28 sessions in rowing ergometer for 30 minutes at 65%–70% of VO\textsubscript{peak} during 8 weeks</td>
<td>↓ matrix metalloprotease</td>
</tr>
<tr>
<td>Tanahashi et al. (2014) (77)</td>
<td>Postmenopausal women: Control (N=10) and exercise group (N=20)</td>
<td>Cycling or walk (2-3 sessions per week initially with 30 minutes/day at 60% of maximal heart rate, and after, 40–60 minutes/day at 65%–80% of maximal heart rate) during 12 weeks</td>
<td>↑ carotid arterial compliance ↓ asymmetric dimethylarginine</td>
</tr>
<tr>
<td>Vezzoli et al. (2014) (80)</td>
<td>Long-distance masters runners (N=20)</td>
<td>Continuous moderate-intensity training: i) 64.5 minutes at 70% gas exchange threshold (GET); ii) 58.5 minutes at 80% GET and iii) 54 minutes at 90% GET during 8 weeks</td>
<td>↓ thiobarbituric acid reactive ↓ total antioxidant capacity ↓ 8-OH-dG</td>
</tr>
<tr>
<td>Radom-Aizik et al. (2014) (83)</td>
<td>Healthy young men (N=12)</td>
<td>High-intensity interval training (10 bouts of 2 minutes with 1 minute of rest interval between sprints) in acute session</td>
<td>↓ Monocyte ↓ TNF-α ↓ TLR4 ↓ CD36 genes</td>
</tr>
<tr>
<td>Suboc et al. (2014) (89)</td>
<td>Sedentary older adults (N=114)</td>
<td>10,000 steps/day during 12 weeks</td>
<td>↑ brachial flow-mediated dilation</td>
</tr>
<tr>
<td>Kitzman et al. (2013) (88)</td>
<td>Older patients with heart failure and preserved ejection fraction (N=63)</td>
<td>Endurance exercise training (3x /week; 60 minutes initially at 40-50% of heart rate reserve walking (5-10 min) and ergometry (5-10 min), and next, the intensity increased gradually until 70% heart rate reserve) during 16 weeks</td>
<td>↑ VO\textsubscript{peak} ↑ quality of life ↔ flow-mediated arterial dilation ↔ ventricular systolic and diastolic function ↔ carotid arterial distensibility</td>
</tr>
<tr>
<td>Nyberg et al. (2012) (73)</td>
<td>Young sedentary (N=8) Older lifelong sedentary (OLS) (N=8) Older lifelong actives (OLA) (N=8)</td>
<td>N-acetylcysteine infusion and knee-extensor exercise (10 minutes with 12 watts and next with a relative workload corresponding 45% W\textsubscript{max}</td>
<td>OLS: ↓ leg blood flow ↓ leg oxygen uptake OLA: ↑ eNOS ↑ NO ↑ ACh response</td>
</tr>
</tbody>
</table>
Hsp90 is a regulator of eNOS activity and coupling. The authors suggested that concentration in both ages after ST but not a significant difference in sedentary or trained rats and observed increases in Hsp90 concentration in the myocardium and skeletal muscle [86, 87].

Lesniewski et al. (2011) [84] compared the effects of eccentric and concentric exercise. In addition, the authors suggest that the benefits of exercise were not restricted to the muscles, but extended to other tissues.

Maeda et al. (2004) [72] demonstrated the effects of high-intensity ST (80% of 1RM) and lower intensity ST (50% of 1 RM), using 1 set of 10 repetitions, 10 exercises and 90 s rest interval between exercises during 12 weeks in older adults aged between 59-69 years and observed that high-intensity ST promoted higher postexercise hypotension and lower forearm vascular resistance in hypertensive elderly subjects (59-69 years old) and concluded that ST with higher volume was more efficient than lower volume to induce vascular benefits in hypertensive elderly patients. In addition, Brito et al. [91] demonstrated the effects of high-intensity ST (80% of 1RM) and lower intensity ST (50% of 1 RM), using 1 set of 10 repetitions, 10 exercises and 90 s rest interval between exercises during 12 weeks in older aged between 59-69 years and observed that high-intensity ST promoted higher postexercise hypotension and lower forearm vascular resistance than low intensity ST.

Regarding to the volume and intensity during ST, Brito et al. [90] verified the effects of two different volumes (1 set vs 3 sets, 50% of 1RM, 10 repetitions, 10 exercises with 90 sec interval recovery) on post-exercise hypotension, forearm blood flow, and forearm vascular resistance in hypertensive elderly subjects (59-69 years old) and concluded that ST with higher volume was more efficient than lower volume to induce vascular benefits in hypertensive elderly patients. In addition, Brito et al. [91] demonstrated the effects of high-intensity ST (80% of 1RM) and lower intensity ST (50% of 1 RM), using 1 set of 10 repetitions, 10 exercises and 90 s rest interval between exercises during 12 weeks in older aged between 59-69 years and observed that high-intensity ST promoted higher postexercise hypotension and lower forearm vascular resistance than low intensity ST.

Donato et al. [92] compared the effects of submaximal forearm handgrip exercise with placebo or an antioxidant cocktail in young men (mean age = 26 year) and older men (mean age = 71 year). Both groups performed a single-leg knee-extensor exercise training with two different intensities (high-intensity ST= 5-10 min at 70-95% of maximal work rate tested on the knee-extensor ergometer; low-intensity ST= 15-45 min at 40-65% of maximal work rate). The brachial artery of older individuals vasodilated less than that in young individuals during submaximal exercise. In older group, ST induced an imbalance between pro- and anti-oxidants, resulting in a greater reliance on free radical-mediated vasodilation. However,
chronic exercise training is capable of restoring oxidant equilibrium and improving vascular function, as observed in the young group.

In relation to the period of recovery between sets, studies from our group have compared 30 seconds versus 90 seconds in healthy adults after 4 sets of squat and 4 sets of bench press, using 70% of the 1 RM until movement failure. We demonstrated that 90 seconds of recovery in response to an acute bout of exhaustive strength exercise induced an increase in IL-6 and IL-10 [93], which may reduce inflammation and improve insulin sensitivity [94]. Heavens et al. [95] showed an increase in IL-6 immediately post exercise and 15 minutes post exercise in young men and women performing a 10 set descending pyramid of squat, bench press, and deadlift (First set= 10 reps and finishing at 1 rep with minimal resting).

Our group also investigated the effect of short (30-sec) and moderate (90-sec) recovery intervals on lipid profile and PAI-1 concentration to exhaustive strength exercise in recreational weightlifters (data not published) and observed that only moderate recovery periods decreased PAI-1 in these subjects. Intra-set rest periods are an important variable to be considered when planning a training protocol, and although the effects of varying rest periods in different kinds of training on vascular aging has yet to be reported, it appears that longer recovery periods that allow for higher workloads lead to a greater anti-inflammatory myokine response.

Thus, manipulating the different ST variables can acutely promote anti-inflammatory adaptations and modulate vascular function during the aging process (Table 2). Strength training is a novel therapy in modulating the vascular aging process, and other training models are currently being investigated in order to find the “best practice”. The next section will discuss modes of exercise less studied that may confer benefits during vascular aging.

4. ALTERNATIVE MODES OF EXERCISE TRAINING

In addition to traditional models of training (aerobic and strength) that show endothelial benefits, alternative training programs or combining different methods may also be employed to promote healthy vascular aging (Table 3).

Rowing requires strength as well as high aerobic and anaerobic capacities. Cook et al. [96] compared habitual rowers with sedentary subjects and showed that rowers have higher central arterial compliance and lower carotid β-stiffness index than the sedentary group. Tai Chi, on the other hand, has a very low anaerobic component and requires participants to meditate while holding isometric positions known as “poses”. Lu et al. [97] compared older Tai Chi practitioners with an older healthy control group and demonstrated superior hemodynamic parameters, as indexed by greater large and small artery compliance in practitioners compared with controls. Thus, it appears that exercise from a wide range of intensity and requirements (i.e.: very high intensity generating high concentrations of blood lactate to very low intensity meditation focused exercise) are available strategies to improve cardiovascular function.

Strength training has been shown in some, but not all studies, to negatively influence central arterial compliance [98]. Concurrent training involves performing both strength training and aerobic training in either the same exercise session or same week, and has been suggested to prevent any reductions in central arterial compliance. Cortez-Cooper et al. [99] compared 13 weeks of strength training or concurrent training (ST= 1 set of 8-12 repetition, 10 exercise with 2-3 minutes of intervals recovery, 3 days/week for 30-45 minutes; Aerobic training= walking or cycling at 60-75% of heart rate reserve, 2 days/week during 30-45 min) in sedentary men and women. After 13 weeks there were no significant differences over time or between groups in carotid artery compliance, carotid-femoral pulse wave velocity, plasma vasoconstrictor hormones, or carotid artery vasoreactivity. These results corroborate a previous meta-analysis that reported no negative effects of strength training on central compliance [98].

Concurrent training may also be an effective physiotherapy in patients with chronic stable coronary artery disease. Gagliardi et al. [100] demonstrated significant increases in VEGF concentrations after 1 month of an exercise program performed twice a week in a rehabilitation center and once a week at the patient’s home that incorporated calisthenics, biking with and without workload, walking, strength exercise or recreational activity in chronic stable coronary artery patients.

Swimming may be a preferred mode of aerobic training in individuals with injuries or joint degenerative diseases compared to walking or running due to the minimization of impact, however, its effects on vascular risks are only recently being investigated. Nualnim et al. [101] evaluated the effect of 12 weeks of swimming exercise (First phase: 15 to 20 minutes/day, 3 to 4 days/week about 60% of maximal heart rate; second phase: 40 to 45 minutes/day, 3 to 4 days/week about 70% to 75% of maximal heart rate) in healthy adults (mean age = 60 years old) and observed a 21% increase in carotid artery compliance, improved flow-mediated dilation and cardiovagal baroreflex sensitivity, and 4 mmHg reduction in systolic blood pressure. Alkatan et al. [102] compared the effects of 12 weeks of swimming or cycling (First phase: 20 to 30 minutes/day, 3 days/week, 40% to 50% of heart rate reserve; second phase: 40 to 45 minutes/day, 3 days/week, 60% to 70% of heart rate reserve) in patients with osteoarthritis and observed that only swimming increased brachial flow-mediated dilation, but both programs decreased hemoglobin and interleukin-6 concentration. Thus, swimming may be a viable strategy to improve vascular function in patients with osteoarthritis or joint injuries.

In summary, the consequences of stress responses induced by different kinds of exercise programs or sports are known to downregulate vascular inflammation and protect vessels from injury, resulting in improved overall health and protection against chronic diseases. However, more research is needed to elucidate how the different variables of training should be manipulated to potentiate the benefits on the endothelial function and inflammation.

5. EXERCISE AND VASCULAR AGING: NEW PERSPECTIVES

Emerging therapeutic strategies include alternative exercise programs [103] or pharmacological agents [104] which have the potential to promote benefits in vascular health have been discussed in the literature. In particular, vascular aging is associated with dysregulation of TNF-α expression, and thus chronic anti-TNF-α treatment, which binds and inactivates TNF-α can result in vasoprotective effects via the downregulation of NADPH oxidases, decreased endothelial apoptosis, and improved endothelial function [105].

It is known that regular exercise increases shear stress which increases mitochondrial biogenesis, upregulates mitochondrial antioxidant system, and induces anti-inflammatory actions such as suppression of TNF-α, and thereby may offer protection against TNF-α-induced vascular impairment [106]. In the last decade blood flow restriction, also known as occlusion or KAATSU training [107], combined with low-intensity strength training (20-30% 1RM) has been shown to increase muscle size and strength in the elderly [108, 109]. This training model requires the use of cuffs that are placed at the proximal ends of the upper arms or thighs by restricting blood flow from the muscle (~100-200 mmHg). Thus, the external pressure applied is sufficient to maintain arterial inflow whilst occluding venous outflow of blood distal to the occlusion site [110], resulting in an ischemic/hypoxic environment that enhances the training effect in exercising muscle [111].

KAATSU training also was investigated with an aerobic training model (20 minutes of treadmill slow walking at 67m per minute, 5 days per week for 6 weeks). Slow walking with blood flow restriction performed by sixteen older women (aged 59-78 years)
Table 2. Strength training-induced alterations on markers related to vascular aging.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Sample</th>
<th>Exercise protocol</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rossi et al. (2016)</td>
<td>Healthy adults (N=8)</td>
<td>Compared 30 seconds versus 90 seconds (4 sets of squat and 4 sets of bench press, using 70% of the 1 RM until movement failure)</td>
<td>†IL-6 and IL-10 after 90 seconds</td>
</tr>
<tr>
<td>Heavens et al. (2014)</td>
<td>Resistance-trained men (N= 9) and women (N= 9)</td>
<td>10 set descending pyramid of squat, bench press, and deadlift (First set= 10 reps and finishing at 1 rep with minimal resting).</td>
<td>†IL-6, †Myoglobin</td>
</tr>
<tr>
<td>Rodrigues et al. (2014)</td>
<td>Patients with peripheral artery disease (N=17)</td>
<td>Single bout (3 series of 10 repetitions and 8 exercises, 5–7 in the OMNI-RES scale, 2 min of resting intervals between sets)</td>
<td>†blood pressure and cardiac work for one hour after exercise</td>
</tr>
<tr>
<td>Rossow et al. (2014)</td>
<td>Young and older women (N=29)</td>
<td>8 weeks of high-intensity ST (3 sets, 8-10 repetitions, 80% of 1RM, 60 s of rest between sets, 3 times/week)</td>
<td>†peak forearm blood flow older subjects ↔ carotid–femoral or femoral-tibialis posterior arterial stiffness</td>
</tr>
<tr>
<td>Brito et al. (2014)</td>
<td>Hypertensive elderly subjects (N=10).</td>
<td>Two different volumes (1 set vs 3 sets, 50% of 1RM, 10 repetitions, 10 exercises with 90 sec interval recovery).</td>
<td>†Post-exercise hypotension in 3 sets; †forearm blood flow in 3 sets, †forearm vascular resistance in 3 sets.</td>
</tr>
<tr>
<td>Brito et al. (2014)</td>
<td>Hypertensive elderly subjects (N=10).</td>
<td>Compared high-intensity ST (80% of 1RM) and (50% of 1 RM), using 1 set of 10 repetitions, 10 exercises and 90 s rest interval between exercises during 12 weeks.</td>
<td>†postexercise hypotension in high-intensity; †forearm vascular resistance in high-intensity.</td>
</tr>
<tr>
<td>Lollo et al. (2013)</td>
<td>Male Wistar rats: control non-exercised, Uphill, downhill, control – horizontal motion, or no inclination.</td>
<td>Run on a treadmill for 35 minutes at a constant speed of 15 m-min⁻¹. Uphill (predominantly concentric contraction) inclination (+7°); downhill (predominantly eccentric contraction) inclination (-7°); control – horizontal motion, or no inclination.</td>
<td>†HSP70 in concentric exercise than eccentric or concentric-eccentric exercise.</td>
</tr>
<tr>
<td>Queiroz et al. (2013)</td>
<td>Men and women (N=16).</td>
<td>3 sets of 8-12 RM, 2-3 min of resting intervals between sets, 9 exercises.</td>
<td>†heart rate and rate-pressure product for up to 4.5 h post-training.</td>
</tr>
<tr>
<td>Park et al. (2012)</td>
<td>Male Fischer: young sedentary, old sedentary, young trained, and old trained (N=344).</td>
<td>Rats in the training groups were habilitated to walk on a motor-driven treadmill at 10 m/min (0° incline) for several minutes, and then speed was increased to 15 m/min, 5 min/day, for 3 days. After habituation, the rats performed treadmill exercise at 15 m/min on a 15° incline, 60 min/day, 5 days/wk, for 10–12 wk.</td>
<td>†angiotensin-induced vasoconstriction.</td>
</tr>
<tr>
<td>Harris et al. (2010)</td>
<td>Young sedentary or trained and older sedentary or trained rats (N=344).</td>
<td>Climbing a 1 m wire ladder, at an 85° angle, 3 days/week, during 6 weeks with increasing weight added to the tail.</td>
<td>†Hsp90 in both age; ↔ eNOS phosphorylation and expression.</td>
</tr>
<tr>
<td>Dobrosielski et al. (2009)</td>
<td>Men (N=12)</td>
<td>Unilateral handgrip training protocol (non-dominant arm, 60% of maximal voluntary handgrip strength, 4 day/week, 20 min per session, and a cadence of 1 contraction per 4 seconds during 1 month).</td>
<td>†45% on brachial artery reactivity.</td>
</tr>
<tr>
<td>Donato et al. (2010)</td>
<td>Young men and older men (N=28)</td>
<td>A single-leg knee-extensor exercise training (high-intensity ST= 5–10 min at 70–95% of maximal work rate tested on the knee-extensor ergometer; low-intensity ST= 15–45 min at 40–65% of maximal work rate).</td>
<td>†brachial artery vasodilated in older; †brachial artery vasodilation after protocols.</td>
</tr>
<tr>
<td>Gonzales et al. (2009)</td>
<td>Young adults and older adults men and women.</td>
<td>Compared age or sex differences in common femoral artery (CFA) shear rates during single-leg knee extensor exercise.</td>
<td>† shear rates in older adults than young. † shear rate in men than women.</td>
</tr>
</tbody>
</table>
(Table 2) Contd….

<table>
<thead>
<tr>
<th>Author (year)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Poelkens et al. (2007) (51)</td>
<td>Elderly men (N=12)</td>
<td>10 weeks of unilateral arm and leg resistance training (3 times a week, 1 hour per session in leg curls, knee extensions, biceps curls, and tricep extensions. First: 1 set, 8–10 repetitions, ~50% of maximal performance; Second: By the end of the third week, 3 sets, ~80% of maximal performance.</td>
<td>↓ resting heart rate; ↑ glucose; ↑ carotid artery peak blood flow; ↔ peripheral and central arterial compliance</td>
</tr>
<tr>
<td>Anton et al. (2006) (44)</td>
<td>Sedentary middle-aged (N=26)</td>
<td>1 set to concentric failure in 12 repetition, about 75% of 1 RM, 2-min intervals recovery, 3 times per week, during 13 wks.</td>
<td>↑ basal femoral blood flow; vascular conductance ↔ brachial blood pressure, plasma endothelin-1 and angiotensin II</td>
</tr>
<tr>
<td>de Jong et al. (2006) (47)</td>
<td>Men with coronary artery disease (N=14)</td>
<td>1 set of 10 repetitions with 60 seconds of recovery intervals and 8 exercises.</td>
<td>↑ t-PA ↓ PAI-1</td>
</tr>
<tr>
<td>Miyachi et al. (2005) (42)</td>
<td>Young and middle-age sedentary or resistance trained (N=104)</td>
<td>Compared young and middle-age, sedentary or resistance trained. All resistance-trained men have been performing moderate- to high-intensity for &gt; 2 yr.</td>
<td>↑ basal whole leg blood</td>
</tr>
<tr>
<td>Panton et al. (2001) (52)</td>
<td>Elderly subjects: Control and resistance training (N=21)</td>
<td>12 weeks (3 sets of 8-12 repetitions, 60-80% 1 RM, 3 times/week, using 10 different exercises)</td>
<td>↑ muscle strength and size; ↔ forearm blood flow; ↔ forearm vascular conductance; ↔ mean arterial pressure; ↔ heart-rate responses to submaximal lower body negative pressure</td>
</tr>
<tr>
<td>Rossi et al. (data not published)</td>
<td>Recreational weightlifters (N=7)</td>
<td>Compared 30 seconds versus 90 seconds (4 sets of squat and 4 sets of bench press, using 90% of the 1 RM until movement failure)</td>
<td>↓ PAI-1</td>
</tr>
</tbody>
</table>

Legend: IL-6= interleukins-6 ; IL-10= interleukins-10; HSP70= heat shock proteins-70; eNOS= endothelial nitric oxide synthase; t-PA= tissue-type plasminogen activator ; PAI-1= plasminogen activator inhibitor-1.

Table 3. Different types of training-induced alterations on markers related to vascular aging.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Sample</th>
<th>Exercise protocol</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkatan et al. (2016) (102)</td>
<td>Patients with osteoarthritis (N=48)</td>
<td>12 weeks of swimming or cycling (First phase: 20 to 30 minutes/day, 3 days/week, 40% to 50% of heart rate reserve; second phase: 40 to 45 minutes/day, 3 days/week, 60% to 70% of heart rate reserve)</td>
<td>↑ brachial flow-mediated dilation only in swimming, ↓ hemoglobin and interleukin-6 concentration in both programs</td>
</tr>
<tr>
<td>Gagliardi et al. (2015) (99)</td>
<td>Patients with chronic stable coronary artery disease (N=21)</td>
<td>1 month of an exercise program performed twice a week in a rehabilitation center and once a week at the patient’s home that incorporated calisthenics, biking with and without workload, walking, strength exercise or recreational activity.</td>
<td>↑ VEGF</td>
</tr>
<tr>
<td>Nualnim et al. (2012) (101)</td>
<td>Healthy adults (mean age = 60 yr) (N=43)</td>
<td>12 weeks of swimming (First phase: 15 to 20 minutes/day, 3 to 4 days/week about 60% of maximal heart rate; second phase: 40 to 45 minutes/day, 3 to 4 days/week about 70% to 75% of maximal heart rate)</td>
<td>↑ carotid artery compliance, ↑ flow-mediated dilation ↓ cardiovascular baroreflex sensitivity ↓ systolic blood pressure</td>
</tr>
<tr>
<td>Ogawa et al. (2010) (100)</td>
<td>Elderly women (mean age= 85 yr) (N=21)</td>
<td>12 weeks of ST (1 set of 10 repetitions was performed for the foot press, front traction, and shoulder press; 2 set of 10 repetitions were performed for vertical traction using elastic cables, 30 minutes per day and intensity was increased according requested by subjects).</td>
<td>↑ muscle thickness, ↓ CRP, ↓ serum amyloid A, ↓ HSP70</td>
</tr>
</tbody>
</table>
### (Table 3) Contd….

<table>
<thead>
<tr>
<th>Author (year)</th>
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<th>Exercise protocol</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lu et al. (2009) (96)</td>
<td>Tai Chi practitioners (N=29), Healthy control subjects (N=36)</td>
<td>Tai Chi practitioners (a minimum of 1.5 hour per week for at least 3 years (average Tai Chi experience 6.7±4.6 years). Control group without previous Tai Chi experience were recruited from elderly centres (morning walk, leisure hiking, or household work).</td>
<td>↑artery compliance in Tai Chi group, ↑ muscle strength in Tai Chi group</td>
</tr>
<tr>
<td>Cortez-Cooper et al. (2008) (98)</td>
<td>Healthy sedentary men and women (N=37), stretching exercises as a control group (n=12)</td>
<td>13 weeks of ST or ST plus aerobic training (ST= 1 set of 8-12 repetitions, 10 exercise with 2-3 minutes of intervals recovery, 3 days/week during 30-45 minutes; Aerobic training= walking or cycling at 60–75% of heart rate reserve, 2 days/week during 30–45 min).</td>
<td>↔ carotid artery compliance; ↔ carotid-femoral pulse wave velocity; ↔ plasma vasoconstrictor hormones; ↔ carotid artery vasoreactivity; ↑ muscle strength and total lean mass in both protocols.</td>
</tr>
</tbody>
</table>

Legend: VEGF= vascular endothelial growth factor; CRP= C-reactive protein; HSP70= heat shock proteins-70.

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**Figure 2. Immunometabolic adaptations by strength training associated with vascular occlusion**

![Immunometabolic adaptations](image)

**Fig. (2).** Immunometabolic adaptations by strength training associated with occlusion.

Increased leg venous compliance and maximal venous outflow, demonstrating for the first time that 6 weeks of walking exercise with blood flow restriction may improve limb venous compliance in untrained elderly female subjects [112]. Many elderly adults may not have the muscular strength or exercise tolerance to train at intensities required to improve compliance, and thus KAATSU training that requires very low intensities may be a viable alternative.

Larkin et al. [113] investigated the effects of 120 unilateral knee extensions at 40% of 1 RM with and without blood flow restriction in healthy young adults. Blood flow restriction resulted in an increase in hemoglobin, transcript expression of VEGF, VEGF-R2, hypoxia inducible factor 1 alpha, NOS, and neuronal NOS. Furthermore, blood flow restriction increased VEGF mRNA at 4 hours post-exercise. This suggests that low intensity strength training with blood flow restriction may increase skeletal muscle angiogenesis and also improve vascular performance. In Figure 2 the main responses mediated by blood flow restriction are illustrated.

Metabolic stress during exercise, as a result of the ischemic/hypoxic environment [114] is hypothesized to induce muscle growth and increase the production of reactive oxygen species (ROS) [115]. Varady et al. [116] demonstrated that an acute strength training can increase adiponectin by 30%-37% in weight...
lifters but not in sedentary subjects. The blood flow and vasodilator actions of adiponectin increase glucose disposal and production of NO in endothelial cells using phosphatidylinositol 3-kinase-dependent pathways involving phosphorylation of eNOS at Ser1179 by AMPK [117]. These anti-inflammatory effects seems to be mediated through the suppression of TLR pathway thus decreasing NF-κB activity [118]. Moreover, adiponectin treatment in cultured macrophages suppresses interferon-γ (IFN-γ) production and increases IL-10 and IL-1ra release even with lipopolysaccharide (LPS) stimuli [119]. In cultured adipocytes adiponectin significantly decreased LPS-induced mRNA IL-6 and mRNA MCP-1 and increases PPARgamma2 expression [120]. Cultures pretreated with adiponectin suppressed the NF-κB response by 40% when LPS was applied compared to LPS alone [121]. Therefore, the increase in adiponectin concentration induced by ischemic/hypoxic and higher metabolic demand during the blood flow restriction plus exercise may be an important strategy to minimizing oxidative stress and providing vaso-protective effects.

CONCLUSION
Exercise training of various durations and intensities appears to prevent and restore the age-related impairment of endothelial function, likely through the restoration of NO availability, reduction in oxidative stress, and a reduced inflammatory environment [103]. Therefore, regardless of the type of exercise, an active lifestyle can increase the release of NO and decrease the turnover of the apoptotic process in the endothelium, thus minimizing vascular inflammation and decreasing the formation of atherosclerotic plaques. However, the difference between exercise protocols used in the literature, as well as the time of the clinical trials, the small sample size, different levels of physical fitness or disease progression, age, and gender should be considered when interpreting and making comparisons between studies regarding the changes induced by exercise on vascular aging. Future studies are therefore necessary to investigate the effects manipulating different variables of training, such as intensity, volume, types of exercise (i.e. blood flow restriction, HIIT, heating), frequency, repetition speed, recovery interval, and the interaction with nutritional interventions on endothelial function and aging.

CONFLICT OF INTEREST
The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS
Declared none.

REFERENCES
Regular Physical Activity and Vascular Aging


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Regular Physical Activity and Vascular Aging


