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Aerobic exercise and other healthy lifestyle factors that influence vascular aging

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Santos-Parker JR, LaRocca TJ, Seals DR. Aerobic exercise and other healthy lifestyle factors that influence vascular aging. *Adv Physiol Educ* 38: 296–307, 2014; doi:10.1152/advan.00088.2014.—Cardiovascular diseases (CVDs) remain the leading cause of death in the United States and other modern societies. Advancing age is the major risk factor for CVD, primarily due to stiffening of the large elastic arteries and the development of vascular endothelial dysfunction. In contrast, regular aerobic exercise protects against the development of large elastic artery stiffness and vascular endothelial dysfunction with advancing age. Moreover, aerobic exercise interventions reduce arterial stiffness and restore vascular endothelial function in previously sedentary middle-aged/older adults. Aerobic exercise exerts its beneficial effects on arterial function by modulating structural proteins, reducing oxidative stress and inflammation, and restoring nitric oxide bioavailability. Aerobic exercise may also promote "resistance" against factors that reduce vascular function and increase CVD risk with age. Preventing excessive increases in abdominal adiposity, following healthy dietary practices, maintaining a low CVD risk factor profile, and, possibly, selective use of pharmaceuticals and nutraceuticals also play a major role in preserving vascular function with aging.

arterial stiffness; endothelial dysfunction; oxidative stress; inflammation

CARDIOVASCULAR DISEASES (CVDs) are the leading cause of morbidity and mortality in modern societies. Advancing age is the primary risk factor for CVD, with >90% of CVD occurring in middle-aged/older (MA/O) adults (58, 86). With the aging of the "baby boomer" generation (adults born between 1946 and 1964), the number of older adults in the United States is expected to double between now and 2050 (110a). As a result, a new epidemic of "boomer-driven" CVDs is projected during this period. Indeed, a 2011 American Heart Association policy statement predicted that without effective intervention, largely as a result of population aging, 40% of United States adults will have one or more forms of CVD by 2030 and medical costs will triple (41). To address this impending biomedical challenge, it will be essential to identify and implement preventive strategies and interventions that will delay and reverse the development of CVD.

Aging leads to increased risk of CVD primarily through the development of arterial dysfunction, which is largely attributable to two physiological changes: stiffening of the large elastic arteries (the aorta and carotid arteries) and the development of systemic vascular endothelial dysfunction (50). These changes also contribute to other age-related declines in function, including cognitive and motor impairments (40, 78, 98, 110, 119). In contrast to aging, healthy lifestyle strategies generally have been linked to reduced CVD risk (26). Over the past two decades, our laboratory has studied the effects of regular aerobic exercise, other healthy lifestyle factors, and, more recently, potential alternative/complementary strategies (e.g. nutraceuticals) on vascular aging and the related mechanisms (Fig. 1) (32, 36, 45, 46, 52, 91). In the following sections, we will summarize this work, starting with the basic physiology of each process in question, and then discuss our key findings on the effects of aerobic exercise and other strategies for promoting healthy vascular aging. For additional details, the reader is directed to our recent and earlier reviews of the related topic (20, 91–95).

Large Elastic Artery Stiffness, Aging, and Exercise

Changes with aging. With contraction of the left ventricle (LV), ejection of blood from the heart creates a pressure wave that travels along the aorta at a velocity dependent on the stiffness and thickness of the artery. As the pressure wave moves forward, it encounters resistance due to branching/thinning of the arterial tree. This creates a reflected pressure wave that returns at a velocity dependent on structural properties of the arterial wall (57, 73). In healthy young individuals, the reflected pressure wave returns to the heart during diastole (65). However, with advancing age, the large elastic arteries (e.g., the aorta and carotid arteries) stiffen, resulting in faster velocities for the forward and reflected pressure waves (the latter returning to the heart during systole) (48). This causes an increase in systolic blood pressure with unchanged or decreased diastolic blood pressure as well as a consequent increased pulse pressure (increased pressure pulsatility), which causes microvascular tissue damage, particularly to vulnerable high flow-dependent organs such as the heart, brain, and kidneys (50, 51, 62, 77). Aortic impedance (increased resistance to LV ejection of blood) is also increased, leading to LV hypertrophy and an increased risk of myocardial infarction and heart failure (50, 51, 62).

Assessment. Large elastic arterial stiffness is commonly assessed by measuring aortic pulse wave velocity (aPWV) or local compliance of the carotid artery (Fig. 2, *left*). aPWV, the clinical gold standard method because of its ability to predict future CVD risk (4, 63, 65), is determined by assessing the time delay between pressure waves occurring at proximal and distal sites along the aorta (typically carotid and femoral arteries). The faster the pressure wave travels along the aorta, the stiffer the artery. aPWV increases with advancing age even in nonhypertensive adults free of clinical CVD (4, 50, 107). Carotid artery stiffness is assessed using ultrasonography to image changes in arterial diameter throughout the cardiac cycle while simultaneously measuring changes in arterial pressure by applanation tonometry in the contralateral carotid artery. From these measures, carotid artery compliance (inversely proportional to stiffness) and carotid β-stiffness (directly proportional

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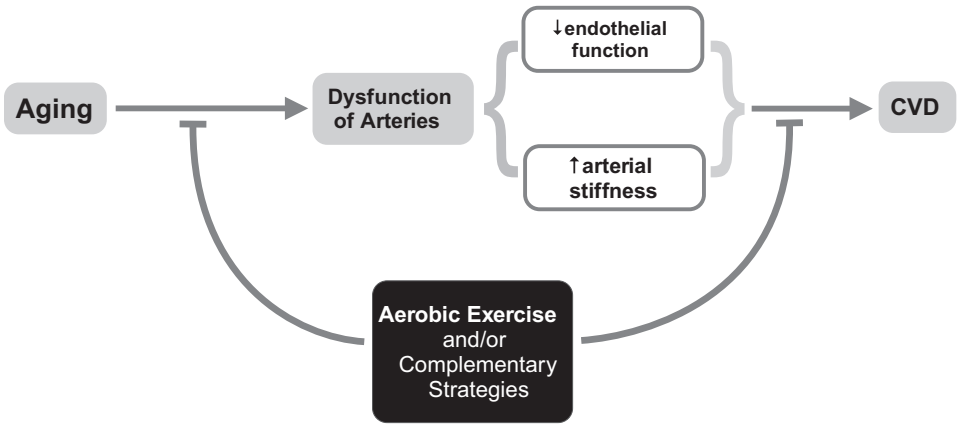

Fig. 1. Aging, arterial dysfunction, and cardiovascular disease (CVD) risk. Aging increases the risk of CVDs through the development of arterial dysfunction (vascular endothelial dysfunction and stiffening of large elastic arteries). As such, aerobic exercise and other evidence-based strategies that either prevent or reverse age-related arterial dysfunction are an important focus for biomedical research. [Modified from Ref. 91.]

to stiffness) can be calculated. Carotid artery compliance decreases with advancing age even in adults free of clinical CVD (69, 108).

Influence of exercise. MA/O men and women who are endurance exercise trained have lower aPWV and greater carotid artery compliance compared with their age-matched sedentary peers (53, 69, 107, 108, 111). Exercise with an aerobic component (e.g., running, swimming, or rowing) is associated with lower large elastic artery stiffness (higher carotid artery compliance) with age compared with sedentary age-matched adults (12, 20, 69, 75, 99, 108), whereas solely resistance exercise-trained MA/O adults demonstrate, if anything, elevated stiffness compared with sedentary control subjects (Table 1) (66). However, MA/O rowers who perform a combination of aerobic- and resistance-based training have reduced arterial stiffness compared with sedentary adults and similar arterial stiffness to their aerobic-exercising peers (12). This suggests that combining aerobic training with resistance training may rescue arterial stiffness and offset the effects of resistance training alone. Importantly, aerobic exercise interventions in MA/O men and women ranging from 12 to 16 wk reduce aPWV and increase carotid artery compliance (Table 1) (39, 69, 99, 108, 125), demonstrating that, in addition to its preventive actions, aerobic exercise also can be viewed as a therapy for destiffening large elastic arteries with aging.

Mechanisms. Age-associated stiffening of the large elastic arteries is mediated by both functional changes involving vascular smooth muscle tone and structural changes in the arterial wall, including extracellular matrix remodeling (increases in collagen deposition and decreases in elastin) and the formation of advanced glycation end products, which cross-link these structural proteins and confer additional stiffening (50, 51, 61, 97). As with functional changes to smooth muscle, structural changes to the arterial wall may be caused and/or sustained by the development of age-related oxidative stress and inflammation (described below) (Fig. 3) (50, 51, 114, 117).

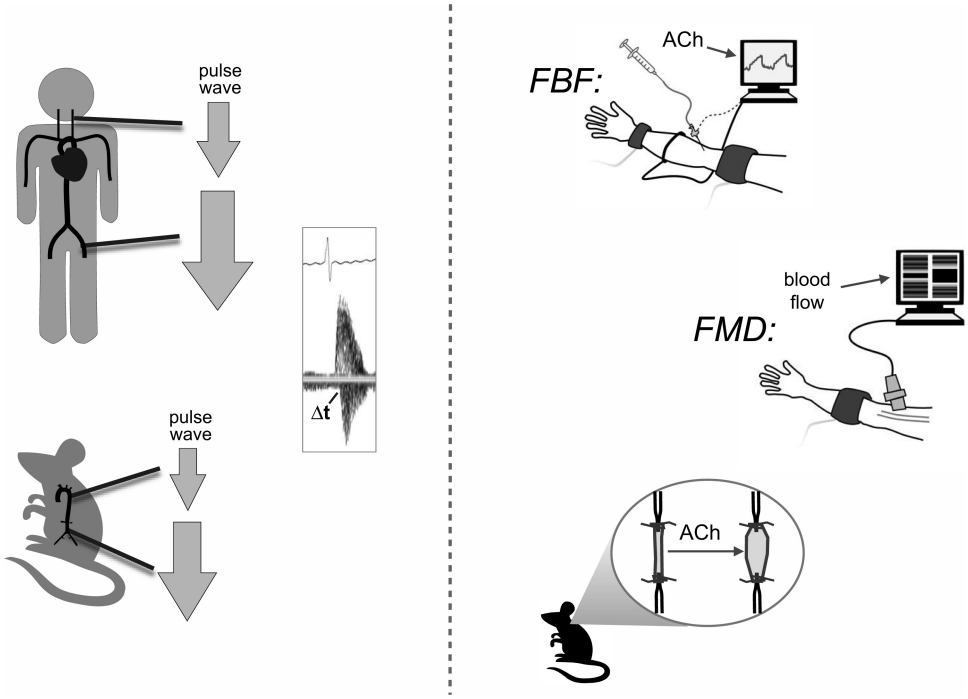

Fig. 2. Assessment of arterial stiffness and vascular endothelial function in human subjects and preclinical rodent models. *Left*: arterial stiffness assessed by measuring the time delay (Δt) between pressure waves at different arterial sites (aortic pulse wave velocity). *Right*: vascular endothelial function assessed by monitoring forearm blood flow (FBF) in response to ACh, measuring brachial artery dilation in response to increased blood flow [flow-mediated dilation (FMD)], or determining ACh-induced changes in arterial diameter in arteries isolated from experimental animals.

Table 1. *Summary of age- and exercise-related differences in arterial stiffness and the mechanisms involved*

	Young Sedentary Subjects	Older Sedentary Subjects	Older Exercising Subjects	Older Sedentary Subjects After Exercise Intervention
Aortic pulse wave velocity	Low (~700 cm/s)	High (~1100 cm/s)	Low (high with resistance training)	Low
Carotid compliance	High (~0.2 mm^2/mmHg)	Low (~0.11 mm^2/mmHg)	High	High
Mechanisms		Structural remodeling	Lack of structural remodeling	Normalization of structural factors
Oxidative stress		↑	↓	↓
Supporting observations				
Collagen		↑*†		↓†
Elastin		↓*†		↔†
Advanced glycation end products		↑*†		↓†
Compliance with vitamin C		↑*	↔*	
Transforming growth factor-β_1				↓†
Nitrotyrosine				↓†

↑, Increase; ↓, decrease. *Humans; †mice.

Studies in human subjects providing mechanistic insight into the effects of aerobic exercise on age-associated large elastic artery stiffening have been limited. Preclinical (rodent) models have played an instrumental role in allowing the assessment of tissues difficult to obtain in humans (e.g., the aorta and carotid arteries), examination of mechanisms involved, and implementation of interventions in a tightly controlled environment within a shorter timeframe. Similarly to humans, rodents demonstrate age-related large elastic artery stiffening (31, 36, 54, 56, 74). In our initial study (31) in mice, we found that 10–14 wk of voluntary wheel running in old previously sedentary animals reduced carotid artery incremental stiffness, consistent with the destiffening effects of swim training previously reported in the aorta of rats (74). Voluntary wheel running also completely reversed nitrotyrosine staining (a cellular footprint of oxidative stress), collagen types I and III, transforming growth factor-β_1 (a profibrotic cytokine), smooth muscle α-actin (a marker of collagen-synthesizing phenotype), and calcification in the artery. However, voluntary wheel running appeared to have no effect on elastin degradation with aging (31). Recent preliminary data from our laboratory have also suggested that voluntary wheel running in old mice reduces aPWV, which is associated with reductions in advanced glycation end product cross-linking of proteins in the aorta (Table 1).

In agreement with the above findings that voluntary wheel running reduces stiffness and oxidative stress in carotid arteries of old mice, acute supraphysiological infusion of the potent antioxidant ascorbic acid (vitamin C) increases carotid artery compliance in sedentary postmenopausal women to levels similar to their endurance exercise-trained counterparts (Table 1) (70). Thus, aerobic exercise may preserve carotid artery compliance in trained postmenopausal women by reducing oxidative stress. These effects of vitamin C have not been observed in sedentary MA/O men (28), suggesting that other factors may contribute to age-related arterial stiffening in men. Collectively, these data from rodent models and studies of human subjects indicate that aerobic exercise may reverse

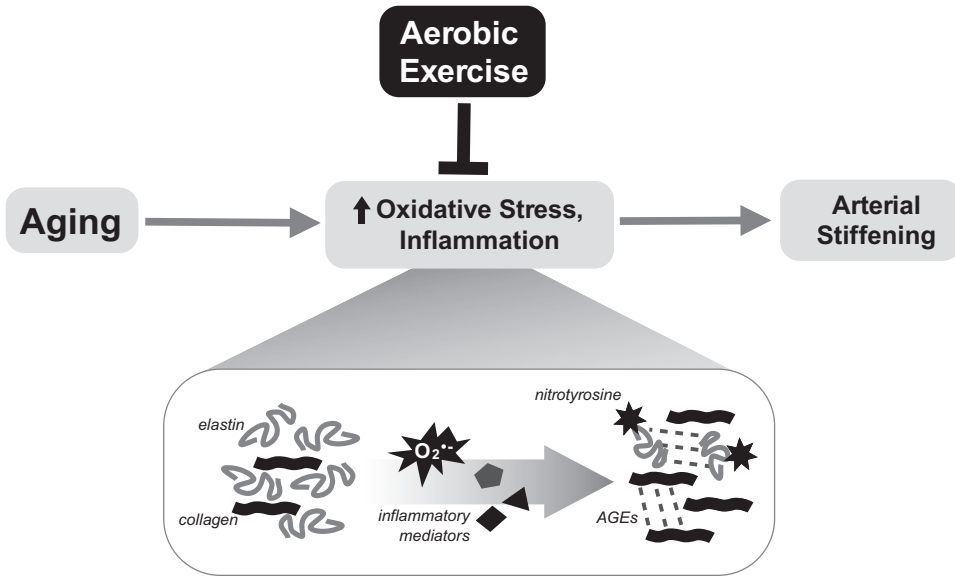

Fig. 3. Structural mechanisms of aging and aerobic exercise on arterial stiffness. Aging induces arterial stiffness in part via structural changes to the arterial wall. Oxidative stress and inflammation involving excessive superoxide ($O_2^{\cdot-}$) production and inflammatory cytokines mediate increases in collagen deposition, fragmentation of elastin, protein oxidation (nitrotyrosine), and formation of advanced glycation end products (AGEs). Aerobic exercise inhibits and/or reverses these age-related changes, resulting in suppression of arterial stiffening.

age-related large elastic artery stiffening by normalizing structural factors and oxidative stress in the artery wall (Fig. 3).

Vascular Endothelial Dysfunction, Aging, and Exercise

Changes with aging. The vascular endothelium consists of a single layer of cells lining the blood vessel walls. In the past, the endothelium was believed to be an inert physical barrier between the blood and arterial wall/surrounding tissue. However, the endothelium is now understood to be a dynamic organ that plays a central role in the control of vascular tone, metabolism, immune function, thrombosis, fibrinolysis, and many other processes (11, 89). Advancing age shifts the endothelium to a prothrombotic, profibrinolytic, proinflammatory, and vasoconstrictive phenotype, individually and collectively characterized as vascular endothelial dysfunction (93, 121). One key cause of age-associated vascular endothelial dysfunction is reduced bioavailability of the vascular protective and vasodilatory molecule nitric oxide (NO) (16, 93, 105, 112, 113).

Assessment. Vascular endothelial function is commonly assessed by measuring endothelium-dependent dilation (EDD), which is the dilation of blood vessels in response to a stimulus (mechanical or chemical) that evokes NO production via the activation of the enzyme endothelial NO synthase (eNOS). NO released by the endothelium diffuses into the surrounding smooth muscle, leading to relaxation and consequent dilation of the artery and increased blood flow that can be measured by several methods (16, 91, 93, 113). The best characterized and most widely used techniques for assessing EDD in humans include *1*) ultrasound assessment of brachial artery dilation in response to an increase in blood flow (mechanical stimulus) produced by temporary forearm ischemia [brachial artery flow-mediated dilation (FMD)] and *2*) increases in forearm blood flow in response to ACh infusion (FBF_{ACh}; pharmacological stimulus) (93). Whereas brachial artery FMD is considered a measure of large muscular artery EDD, FBF_{ACh} is viewed as an indicator of microvascular (resistance vessel) EDD (93). In rodents, isolation of arteries (the aorta, carotid arteries, etc.) to measure the change in dilation in response to ACh incubation (pharmacological stimulus) is used to assess EDD (Fig. 2, *right*) (14, 25, 36, 54, 72). Both brachial artery FMD and FBF_{ACh} are reduced with advancing age even in adults free of major CVD risk factors or clinical disease, indicating endothelial dysfunction as a primary effect of aging (10, 18, 22, 29, 103, 105, 106).

Influence of aerobic exercise on brachial artery FMD. Brachial artery FMD is lower in healthy, sedentary older men compared with young men (10, 29, 33, 82). However, this age-related decline in function is not observed in endurance exercise-trained men (29, 30, 33, 34, 82). Moreover, an intervention consisting of several weeks of brisk walking restores brachial artery FMD in previously sedentary MA/O men to levels similar to young and older endurance exercise-trained subjects (Table 2) (83). However, the effects of aerobic exercise on brachial artery FMD in older (postmenopausal) women remain unclear. Cross-sectional and interventional studies have shown either no differences (9, 80, 101) or greater (1, 6, 37, 100, 124) brachial artery FMD in endurance exercise-trained compared with sedentary postmenopausal women. A recent study (71) from our laboratory found that a 12-wk aerobic exercise intervention increased brachial artery FMD in estrogen-supplemented, but not estrogen-deficient, postmenopausal sedentary women, suggesting that estrogen may play a permissive role in inducing the beneficial effects of aerobic exercise on vascular endothelial function with aging in women (Table 3). Thus, aerobic exercise is consistently associated with enhanced brachial artery FMD with aging in men and estrogen-supplemented women but not in estrogen-deficient women.

Influence of aerobic exercise on changes in FBF_{ACh}. Among healthy men, MA/O subjects have lower FBF_{ACh} compared

Table 2. *Summary of age- and exercise-related differences in vascular endothelial function and the mechanisms involved in men and rodents*

	Young Sedentary Subjects	Older Sedentary Subjects	Older Exercising Subjects	Older Sedentary Subjects After Exercise Intervention
FBF_{ACh}	High (~16 ml·100 ml tissue^{-1}·min^{-1} maximum)	Low (~10 ml·100 ml tissue^{-1}·min^{-1} maximum)	High	High
FMD in the brachial artery	High (~8 % change)	Low (~3 % change)	High (low with resistance training)	High
Mechanisms				
NO		↓	↑	↑
Oxidative stress		↑	↓	↓
Inflammation		↑	↓	↓
Supporting Observations				
EDD		Similar to others with eNOS inhibition	Similar to others with eNOS inhibition	Similar to others with eNOS inhibition
Nitrotyrosine		↑	↓	↓
NADPH oxidase		↑	↓*	↓†
SOD		↓*	↑*	↑†
EDD with Tempol		↑†		↔†
FMD with vitamin C	↔*	↑*	↔*	
NF-κB		↑*†	↓*	↓†
FMD with salsalate	↔*	↑*	↔*	

FBF_{ACh}, forearm blood flow in response to ACh infusion; FMD, flow-mediated dilation; NO, ntiric oxide; EDD, endothelium-dependent dilation; eNOS, endothelial NO synthase. *Humans; †mice.

with young control subjects (18, 102, 104, 106). However, these age-related differences are not observed in young and old endurance exercise-trained men (18, 102). Thus, it appears that aerobic exercise also protects against the development of microvascular endothelial dysfunction with aging in men. Moreover, 12 wk of brisk walking restores FBF_{ACh} in older previously sedentary men to levels similar to young and old endurance exercise-trained men (Table 2) (18), indicating that exercise can be viewed as a therapy in this group. These studies, all in male subjects, demonstrate that greater EDD in young and older exercising men is mediated by greater NO bioavailability, as all group differences were abolished by inhibition of eNOS (infusion of the eNOS inhibitor N^G-monomethyl-L-arginine) (102). However, the effects of aerobic exercise on microvascular EDD (FBF_{ACh}) in postmenopausal women remain unknown.

Influence of exercise characteristics. The type, frequency, intensity, and duration of exercise training required to preserve/improve vascular endothelial function with advancing age is incompletely understood. Endurance exercise-trained MA/O subjects engaged in walking/running type exercise have greater brachial artery FMD than their sedentary counterparts, but this has not been consistently shown for other types of aerobic exercise (cyclists/swimmers) (2, 18, 75, 76, 83, 90, 100, 109, 124). Moreover, the minimal available evidence indicates that resistance training in MA/O subjects does not exert beneficial effects on brachial artery FMD (9). Multiple studies have indicated that at least 3 days of aerobic exercise per week, at a target range of 65–80% of maximal heart rate, for 30–50 min/day, for 2–6 mo elicit improvements in brachial artery FMD (2, 18, 67, 76, 83, 90, 100, 125). Thus, although the data suggest that moderate aerobic exercise is sufficient to preserve/improve EDD with aging in men and, perhaps, selective groups of women, further studies are needed to gain insights into the exact type, frequency, intensity, and duration of exercise training needed.

Mechanisms. More is known about the mechanisms underlying the beneficial effects of aerobic exercise on age-related vascular endothelial dysfunction than arterial stiffness due to more extensive data from preclinical studies and easier access to the endothelium via the peripheral vasculature of humans. Using these models and techniques, oxidative stress and inflammatory signaling have been identified as key pathways involved in modulating vascular endothelial function. With advancing age, these pathways become dysregulated, leading to reduced NO bioavailability and vascular endothelial dysfunction. As explained below, aerobic exercise is believed to preserve/restore vascular endothelial function by reversing age-related oxidative stress and inflammation (Fig. 4) (20, 92–95).

Oxidative stress. Age-related vascular endothelial function is associated with increased oxidative stress, defined as excess bioactivity of ROS relative to antioxidant defenses (93, 94). Key age-related changes that contribute to oxidative stress include increases in superoxide production (by mitochondria, NADPH oxidase, and/or eNOS uncoupling) and decreases in endogenous antioxidant enzyme systems, including SODs (93, 94). Superoxide reduces NO bioavailability by interacting with NO to form peroxynitrite, a potent intermediary ROS. Peroxynitrite causes nitration of tyrosine residues on proteins (nitrotyrosine) and the uncoupling of eNOS, leading to more superoxide production and reduced NO (Fig. 4) (5, 27, 42).

We have performed translational studies in mice and humans to examine the effects of aerobic exercise on age-related oxidative stress in the vasculature. For example, we have found that incubation with the superoxide scavenger Tempol restores EDD in arteries of old sedentary mice but has no effect on young control and old voluntary wheel-running mice (24). Similarly, in older sedentary men, acute infusion of vitamin C restores brachial artery FMD to levels observed in young sedentary and old endurance exercise-trained men (Table 2) (28, 102). Vitamin C infusion also improves FMD in sedentary and aerobic exercise-trained estrogen-deficient postmenopausal women but not in estrogen-supplemented women who participated in an aerobic exercise intervention (Table 3) (71). Collectively, these translational studies suggest that suppression of superoxide-

Table 3. *Summary of age- and exercise-related differences in vascular endothelial function and the mechanisms involved in women*

	Young Sedentary Subjects	Older Sedentary Estrogen-Deficient Subjects	Older Sedentary Estrogen-Supplemented Subjects	Older Exercising Estrogen-Deficient Subjects	Older Exercising Estrogen-Supplemented Subjects	Older Sedentary Estrogen-Deficient Subjects After Exercise Intervention	Older Sedentary Estrogen-Supplemented Subjects After Exercise Intervention
FBF_{Ach}	High (~16 ml/100 ml tissue/min max)	Low (~10 ml/100 ml tissue/min max)	High (some reports: low)				
FMD in the brachial artery	High (~8 % change)	Low (~3 % change)	High (some reports: low)	Low (some reports: high)	High	Low (some reports: high)	High (some reports: low)
Mechanisms							
NO		↓					
Oxidative stress		↑	↑	↑		↑	↓
Inflammation		↑		↓			
Supporting observations							
EDD		Similar to young subjects with eNOS inhibition					
FMD with vitamin C	↔	↑	↑	↑		↑	↔
NF-κB		↑		↓			
FMD with salsalate	↔	↑		↔			

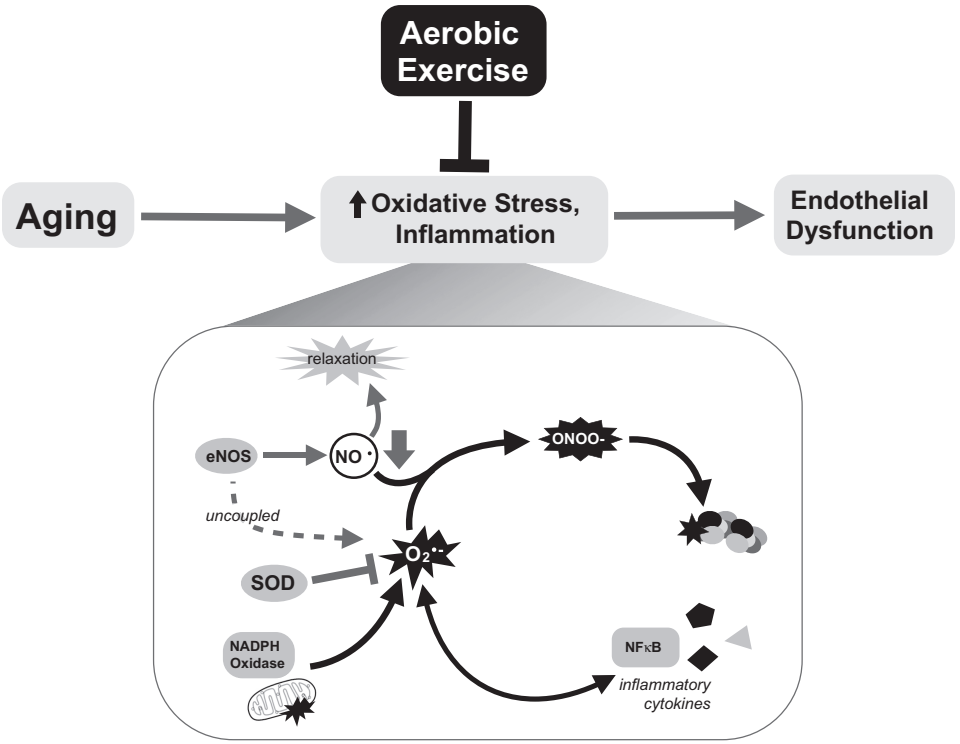

Fig. 4. Mechanisms of aging and aerobic exercise on endothelial function. Aging leads to endothelial dysfunction mediated by vascular oxidative stress and inflammation. Excessive $O_2^{\cdot -}$ production, modulated by NADPH oxidase, SOD, uncoupling of endothelial nitric oxide (NO) synthase (eNOS), and other mechanisms (e.g., dysfunctional mitochondria), is a central mediator of these events. Excessive $O_2^{\cdot -}$ causes peroxynitrite ($ONOO^-$) formation and protein oxidation (nitrotyrosine) as well as the activation of NF-κB and induction of inflammatory cytokines. [Modified from Ref. 91.] Aerobic exercise inhibits and/or reverses these age-related changes, resulting in enhanced endothelial function.

mediated oxidative stress plays a role in the beneficial effects of aerobic exercise on vascular endothelial dysfunction with aging.

Parallel observations in rodent models and human subjects further support the idea that aerobic exercise reduces vascular oxidative stress. For example, 10–14 wk of voluntary wheel running reduces aortic nitrotyrosine and NADPH oxidase ($p67^{phox}$ subunit) expression in old previously sedentary mice (24). Moreover, the NADPH oxidase inhibitor apocynin restores EDD in old sedentary mice to levels similar to young control and old voluntary wheel-running mice but has no effect on the latter groups (24). Similarly, in humans, expression of nitrotyrosine and NADPH oxidase ($p47^{phox}$ subunit) is higher in biopsied vascular endothelial cells from the brachial arteries of older sedentary men than in cells from young sedentary and old endurance exercise-trained men (Table 2) (82).

Whereas differences in arterial NADPH oxidase and nitrotyrosine reflect influences on prooxidant processes, differences in antioxidant capacity with exercise also could contribute to enhanced endothelial function with aging. In old voluntary wheel-running mice, the activities of aortic SODs, including manganese (mitochondrial), copper-zinc (cytosolic), and extracellular SODs, are increased relative to old control (nonrunning) mice (24). Similarly, in humans, expression of manganese SOD in biopsied vascular endothelial cells and activity of circulating (plasma) extracellular SOD are greater in aerobically exercising than in sedentary MA/O men and similar to levels observed in young men (Table 2) (82). Taken together, these observations indicate that advancing age leads to the development of oxidative stress in the vasculature and that aerobic exercise exerts its vascular-protective effects by reducing oxidative stress via suppression of prooxidant and stimulation of antioxidant pathways.

Inflammation. Aging results in the suppression of adaptive immunity and upregulation of innate immune signaling, leading to a phenotype of chronic low-grade inflammation known as "inflammaging" (88). A central mediator of age-associated increases in vascular inflammation is the proinflammatory transcription factor NF-κB (21, 22). Activation of the NF-κB pathway leads to upregulation of proinflammatory cytokines and NADPH oxidase (13, 23, 93, 94). All of these events stimulate additional production of superoxide, which reacts with NO, reducing its bioavailability and further contributing to vascular dysfunction. NF-κB also can be activated by cytokines and ROS, perpetuating this cycle of adverse signaling (Fig. 4) (23).

Studies in rodent models and human subjects have provided evidence showing that aerobic exercise improves EDD by reducing vascular inflammation. Our preclinical work showed that vascular NF-κB expression in old mice that have access to running wheels for 10–14 wk is normalized to levels of young mice. This was associated with lower expression of proinflammatory cytokines along with restored EDD (55). Parallel published (21, 82) and preliminary observations in humans have indicated that cellular expression of inflammatory cytokines (e.g., IL-6) and NF-κB is lower (similar to levels in young) in older endurance exercise-trained men compared with their sedentary counterparts and is associated with preserved brachial artery FMD. When salsalate (a potent NF-κB-inhibiting agent) is given to young control, MA/O sedentary, and MA/O endurance exercise-trained subjects for 4 days, endothelial cell NF-κB expression is reduced and brachial artery FMD is restored in MA/O sedentary subjects to levels similar to MA/O endurance-exercise trained and young subjects, with no effects on the latter groups (Tables 2 and 3) (116). Vitamin C infusion abolishes differences in FMD among these groups, indicating

that these effects of regular aerobic exercise in inhibiting age-related inflammation-associated suppression of brachial artery FMD are mediated by reduced oxidative stress.

In summary, aerobic exercise preserves and restores vascular endothelial function with advancing age. Evidence suggests that the major underlying mechanism is the modulation of oxidative stress and inflammatory pathways.

Exercise: Vascular Protection From "Adverse Factors"

Previously, it was believed that the CVD-preventing effects of aerobic exercise were due solely to its ability to improve traditional risk factors such as blood pressure, plasma lipids, blood glucose, and body weight/fat. However, epidemiological studies (68) indicate that modification of these risk factors only accounts for 50% or less of the CVD risk-lowering effects of aerobic exercise. Our work suggests a complementary hypothesis: aerobic exercise may exert its CVD risk-lowering effects not only by lowering traditional risk factors but also by creating a "resistance" against the harmful effects of existing risk factors as well (95, 115). This idea is supported by our observations on plasma low-density lipoprotein (LDL)-cholesterol, a harmful CVD risk factor, and vascular endothelial function. Older sedentary adults with borderline high LDL-cholesterol have lower brachial artery FMD compared with their counterparts with normal levels of LDL-cholesterol. However, there are no differences in brachial artery FMD among groups of young sedentary and older endurance exercise-trained adults with borderline high or normal LDL-cholesterol, suggesting young age and aerobic exercise protect against the adverse influence of elevated plasma LDL-cholesterol on vascular endothelial function (115). This hypothesis is further supported by the results of our recent study (19) demonstrating that aerobic exercise training in older adults protects against the effects of impaired fasting blood glucose, another adverse factor, on endothelial function. More recently, we demonstrated that old sedentary mice given access to a running wheel for 10–14 wk are protected against "Western" (high fat) diet-induced vascular endothelial dysfunction, and this was mediated by a reduction in superoxide-associated oxidative stress and an increase in NO bioavailability (56). Taken together, these findings suggest aerobic exercise protects aging arteries not only by lowering risk factors but also by inducing a resistance against currently existing harmful levels of risk factors (Fig. 5).

Other Healthy Lifestyle Factors and Vascular Aging

Evidence suggests that other healthy lifestyle behaviors may act through similar pathways to aerobic exercise and, therefore, be alternative (or complementary) strategies for preserving vascular function and health with aging (Fig. 6) (94).

Excessive abdominal adiposity (indicated by waist circumference $>$ 40 in. in men and $>$35 in. in women) is associated with impaired vascular function and increased risk of CVD (3, 15, 47, 118, 122, 127). Consistent with this observation, energy restriction-induced weight loss associated with significant reductions in total and abdominal body fat reverses vascular dysfunction in MA/O adults at least in part by reducing oxidative stress and increasing NO bioavailability (17, 81), a finding that is supported by parallel studies (56, 85, 126) demonstrating that caloric restriction protects against/reverses age-related endothelial dysfunction in rodents. In addition to total daily energy intake, diet composition also has an important modulatory effect on vascular aging. Supplementing normal dietary intake with more fruits and vegetables, and switching to established healthy diets, including the DASH and Mediterranean diets, improve vascular function in MA/O adults (7, 49, 60, 87). Reduced dietary Na^+ intake in MA/O obese or hypertensive adults is associated with greater EDD (brachial artery FMD), reduced large elastic artery stiffness, and increased NO bioavailability as a result of reduced superoxide-associated oxidative stress (35, 44, 45). In general, diets high in K^+, fiber, seeds, whole grains, and nuts and low in Na^+, saturated fats, and cholesterol are associated with enhanced vascular function in groups of MA/O adults (7, 49, 60, 87, 94).

Although healthy lifestyle behaviors appear to be the best method for protecting against vascular aging, many older adults do not meet the minimal recommended guidelines for exercise or consume a healthy diet. As a result, there is significant interest in pharmacological agents, both pharmaceuticals and nutraceuticals (naturally occurring, bioactive food compounds) that may induce some of the same beneficial, vascular-protective effects as healthy lifestyle behaviors (94). Most prescription drugs that improve vascular function in

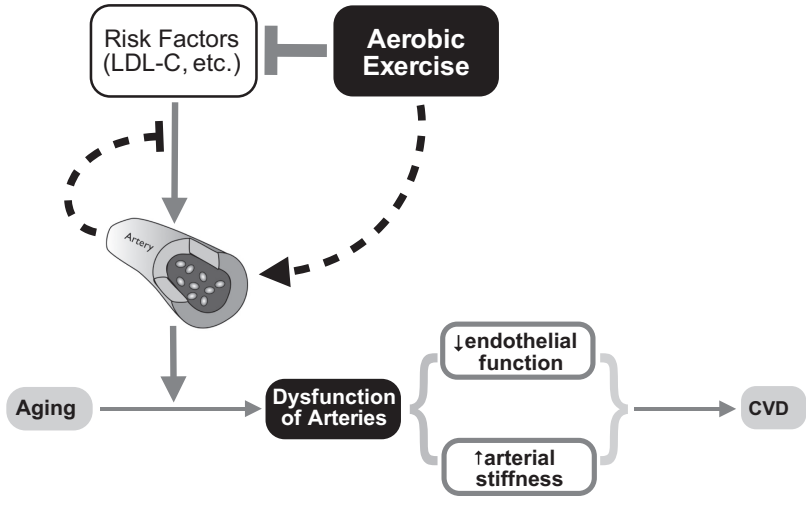

Fig. 5. Aging, aerobic exercise, and adverse risk factors. Aging increases the risk of developing CVDs through stiffening of large elastic arteries and the development of vascular endothelial dysfunction. Aerobic exercise protects against arterial dysfunction not only by directly lowering traditional risk factors [e.g., low-density lipoprotein-cholesterol (LDL-C)] but also by inducing "resistance" against currently existing harmful levels of risk factors.

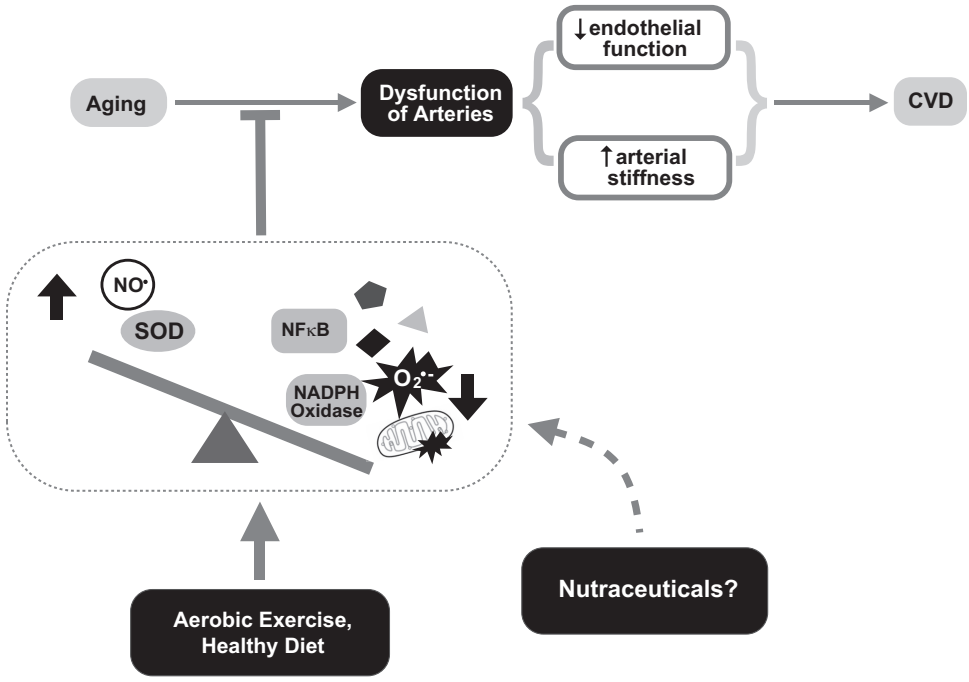

Fig. 6. Aging, aerobic exercise, and other healthy lifestyle strategies. Aerobic exercise as well as other evidence-based complementary strategies (e.g., healthy dietary intake or nutraceuticals) that induce some of the protective effects of exercise by increasing NO bioavailability and antioxidant defenses [SOD, lowering $O_2^{\cdot-}$ production (e.g., by inhibiting NADPH oxidase), and reducing inflammation (i.e., activation of NF-κB and inflammatory cytokines)] serve to preserve vascular function with aging.

humans have been tested in patients with existing clinical cardiometabolic diseases or major risk factors for these disorders and are not indicated for treating vascular aging per se (38, 59, 64, 94, 120). However, certain nutraceutical compounds may activate or inhibit the same signaling pathways as healthy lifestyle behaviors and, therefore, produce at least some of the same beneficial effects. These nutraceutical compounds as an alternative strategy may be appealing for several reasons, including their lower cost to purchase and manufacture, natural origin, and less time-consuming regulatory approval process (compared with new prescription pharmaceuticals). Although many studies in preclinical models and humans are underway to determine the potential vascular protective effects of a variety of these compounds in the context of vascular aging, in general, much more evidence is needed on efficacy in MA/O populations before nutraceuticals can be considered viable alternatives or complements to healthy physical activity and dietary practices.

Recently, our laboratory and others have been conducting exploratory translational investigations on nutraceuticals that target key pathways linked to vascular aging (e.g., oxidative stress and inflammation) that are modulated by aerobic exercise and healthy dietary intake (1, 8, 32, 36, 43, 52, 79, 84, 94, 96, 123). Examples include nitrate/nitrite supplementation (precursors of NO that may boost NO bioavailability and signaling), curcumin (an anti-inflammatory phenol found in the Indian spice turmeric), vitamin D (a fat-soluble vitamin with antioxidant/inflammatory properties), MitoQ (a mitochondria-targeted antioxidant), trehalose (an autophagy-activating disaccharide found commonly in mushrooms and other foods), and sirtuin system activators like resveratrol (1, 8, 32, 36, 43, 52, 79, 84, 94, 96, 123). These agents and other compounds that demonstrate similar ability to prevent/reverse activation of adverse vascular aging processes hold promise for enhancing vascular function and health with advancing age (Fig. 6).

Overall Summary and Conclusions

Vascular aging is the major risk factor for CVD. With the aging of our population, there is a pressing need for preventive strategies and interventions that may reduce the risk of CVD. Aerobic exercise should be considered a "first line" strategy to protect against/reverse stiffening of the large elastic arteries and the development of vascular endothelial dysfunction, in part via favorable modulation of the causal mechanisms of vascular aging: oxidative stress, inflammation, structural changes to the arterial wall, and reduced NO bioavailability. Aerobic exercise not only improves conventional CVD risk factors, thus lessening their impact, but likely induces a resistance against the potentially harmful effects of a number of adverse factors to which our arteries are chronically exposed with advancing age. Other healthy lifestyle practices, including proper management of abdominal adiposity with aging, intake of a vascular-protective diet, and nutraceuticals that may convey at least some of the benefits of exercise and a healthy diet, also may prove helpful for preserving vascular function and preventing age-associated CVD.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: J.R.S.-P., T.L.L., and D.R.S. conception and design of research; J.R.S.-P. drafted manuscript; J.R.S.-P., T.L.L., and D.R.S. edited and revised manuscript; J.R.S.-P., T.L.L., and D.R.S. approved final version of manuscript; T.L.L. prepared figures.

REFERENCES

1. **Akazawa N, Choi Y, Miyaki A, Tanabe Y, Sugawara J, Ajisaka R, Maeda S.** Curcumin ingestion and exercise training improve vascular endothelial function in postmenopausal women. *Nutr Res* 32: 795–799, 2012.
3. **American Heart Association**. *Heart and Stroke Facts*. Dallas, TX: American Heart Association, 1992.
4. **Avolio AP, Deng FQ, Li WQ, Luo YF, Huang ZD, Xing LF, O'Rourke MF.** Effects of aging on arterial distensibility in populations with high and low prevalence of hypertension: comparison between urban and rural communities in China. *Circulation* 71: 202–210, 1985.
5. **Bachschmid MM, Schildknecht S, Matsui R, Zee R, Haeussler D, Cohen RA, Pimental D, Loo B.** Vascular aging: chronic oxidative stress and impairment of redox signaling-consequences for vascular homeostasis and disease. *Ann Med* 45: 17–36, 2013.
6. **Black MA, Cable NT, Thijssen DH, Green DJ.** Impact of age, sex, and exercise on brachial artery flow-mediated dilatation. *Am J Physiol Heart Circ Physiol* 297: H1109–H1116, 2009.
7. **Blumenthal JA, Babyak MA, Hinderliter A, Watkins LL, Craighead L, Lin PH, Caccia C, Johnson J, Waugh R, Sherwood A.** Effects of the DASH diet alone and in combination with exercise and weight loss on blood pressure and cardiovascular biomarkers in men and women with high blood pressure: the ENCORE study. *Arch Intern Med* 170: 126–135, 2010.
8. **Carrizzo A, Puca A, Damato A, Marino M, Franco E, Pompeo F, Traficante A, Civitillo F, Santini L, Trimarco V, Vecchione C.** Resveratrol improves vascular function in patients with hypertension and dyslipidemia by modulating NO metabolism. *Hypertension* 62: 359–366, 2013.
9. **Casey DP, Pierce GL, Howe KS, Mering MC, Braith RW.** Effect of resistance training on arterial wave reflection and brachial artery reactivity in normotensive postmenopausal women. *Eur J Appl Physiol* 100: 403–408, 2007.
10. **Celermajer DS, Sorensen KE, Spiegelhalter DJ, Georgakopoulos D, Robinson J, Deanfield JE.** Aging is associated with endothelial dysfunction in healthy men years before the age-related decline in women. *J Am Coll Cardiol* 24: 471–476, 1994.
11. **Cines DB, Pollak ES, Buck CA, Loscalzo J, Zimmerman GA, McEver RP, Pober JS, Wick TM, Konkle BA, Schwartz BS, Barnathan ES, McCrae KR, Hug BA, Schmidt AM, Stern DM.** Endothelial cells in physiology and in the pathophysiology of vascular disorders. *Blood* 91: 3527–3561, 1998.
12. **Cook JN, DeVan AE, Schleifer JL, Anton MM, Cortez-Cooper MY, Tanaka H.** Arterial compliance of rowers: implications for combined aerobic and strength training on arterial elasticity. *Am J Physiol Heart Circ Physiol* 290: H1596–H1600, 2006.
13. **Csiszar A, Wang M, Lakatta EG, Ungvari Z.** Inflammation and endothelial dysfunction during aging: role of NF-κB. *J Appl Physiol* 105: 1333–1341, 2008.
14. **d'Uscio LV, Smith LA, Katusic ZS.** Hypercholesterolemia impairs endothelium-dependent relaxations in common carotid arteries of apolipoprotein E-deficient mice. *Stroke* 32: 2658–2664, 2001.
15. **de Koning L, Merchant AT, Pogue J, Anand SS.** Waist circumference and waist-to-hip ratio as predictors of cardiovascular events: meta-regression analysis of prospective studies. *Eur Heart J* 28: 850–856, 2007.
16. **Deanfield JE, Halcox JP, Rabelink TJ.** Endothelial function and dysfunction: testing and clinical relevance. *Circulation* 115: 1285–1295, 2007.
17. **Dengo AL, Dennis EA, Orr JS, Marinik EL, Ehrlich E, Davy BM, Davy KP.** Arterial destiffening with weight loss in overweight and obese middle-aged and older adults. *Hypertension* 55: 855–861, 2010.
18. **DeSouza CA, Shapiro LF, Clevenger CM, Dinenno FA, Monahan KD, Tanaka H, Seals DR.** Regular aerobic exercise prevents and restores age-related declines in endothelium-dependent vasodilation in healthy men. *Circulation* 102: 1351–1357, 2000.
19. **DeVan AE, Eskurza I, Pierce GL, Walker AE, Jablonski KL, Kaplon RE, Seals DR.** Regular aerobic exercise protects against impaired fasting plasma glucose-associated vascular endothelial dysfunction with aging. *Clin Sci (Lond)* 124: 325–331, 2013.
20. **DeVan AE, Seals DR.** Vascular health in the ageing athlete. *Exp Physiol* 97: 305–310, 2012.
21. **Donato AJ, Black AD, Jablonski KL, Gano LB, Seals DR.** Aging is associated with greater nuclear NFκB, reduced IκBα, and increased expression of proinflammatory cytokines in vascular endothelial cells of healthy humans. *Aging Cell* 7: 805–812, 2008.
22. **Donato AJ, Eskurza I, Silver AE, Levy AS, Pierce GL, Gates PE, Seals DR.** Direct evidence of endothelial oxidative stress with aging in humans: relation to impaired endothelium-dependent dilation and up-regulation of nuclear factor-κB. *Circ Res* 100: 1659–1666, 2007.
23. **Donato AJ, Pierce GL, Lesniewski LA, Seals DR.** Role of NFκB in age-related vascular endothelial dysfunction in humans. *Aging* 1: 678–680, 2009.
24. **Durrant JR, Seals DR, Connell ML, Russell MJ, Lawson BR, Folian BJ, Donato AJ, Lesniewski LA.** Voluntary wheel running restores endothelial function in conduit arteries of old mice: direct evidence for reduced oxidative stress, increased superoxide dismutase activity and down-regulation of NADPH oxidase. *J Physiol* 587: 3271–3285, 2009.
25. **Eberhardt RT, Forgione MA, Cap A, Leopold JA, Rudd MA, Trolliet M, Heydrick S, Stark R, Klings ES, Moldovan NI, Yaghoubi M, Goldschmidt-Clermont PJ, Farber HW, Cohen R, Loscalzo J.** Endothelial dysfunction in a murine model of mild hyperhomocyst(e)inemia. *J Clin Invest* 106: 483–491, 2000.
26. **Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, Lee IM, Lichtenstein AH, Loria CM, Millen BE, Nonas CA, Sacks FM, Smith SC Jr, Svetkey LP, Wadden TA, Yanovski SZ.** 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 129: S76–S99, 2014.
27. **El Assar M, Angulo J, Vallejo S, Peiro C, Sanchez-Ferrer CF, Rodriguez-Manas L.** Mechanisms involved in the aging-induced vascular dysfunction. *Front Physiol* 3: 132, 2012.
28. **Eskurza I, Monahan KD, Robinson JA, Seals DR.** Ascorbic acid does not affect large elastic artery compliance or central blood pressure in young and older men. *Am J Physiol Heart Circ Physiol* 286: H1528–H1534, 2004.
29. **Eskurza I, Monahan KD, Robinson JA, Seals DR.** Effect of acute and chronic ascorbic acid on flow-mediated dilatation with sedentary and physically active human ageing. *J Physiol* 556: 315–324, 2004.
30. **Eskurza I, Myerburgh LA, Kahn ZD, Seals DR.** Tetrahydrobiopterin augments endothelium-dependent dilatation in sedentary but not in habitually exercising older adults. *J Physiol* 568: 1057–1065, 2005.
31. **Fleenor BS, Marshall KD, Durrant JR, Lesniewski LA, Seals DR.** Arterial stiffening with ageing is associated with transforming growth factor-β1-related changes in adventitial collagen: reversal by aerobic exercise. *J Physiol* 588: 3971–3982, 2010.
32. **Fleenor BS, Sindler AL, Marvi NK, Howell KL, Zigler ML, Yoshizawa M, Seals DR.** Curcumin ameliorates arterial dysfunction and oxidative stress with aging. *Exp Gerontol* 48: 269–276, 2013.
33. **Franzoni F, Ghiadoni L, Galetta F, Plantinga Y, Lubrano V, Huang Y, Salvetti G, Regoli F, Taddei S, Santoro G, Salvetti A.** Physical activity, plasma antioxidant capacity, and endothelium-dependent vasodilation in young and older men. *Am J Hypertens* 18: 510–516, 2005.
34. **Galetta F, Franzoni F, Plantinga Y, Ghiadoni L, Rossi M, Prattichizzo F, Carpi A, Taddei S, Santoro G.** Ambulatory blood pressure monitoring and endothelium-dependent vasodilation in the elderly athletes. *Biomed Pharmacother* 60: 443–447, 2006.
35. **Gates PE, Tanaka H, Hiatt WR, Seals DR.** Dietary sodium restriction rapidly improves large elastic artery compliance in older adults with systolic hypertension. *Hypertension* 44: 35–41, 2004.
36. **Gioscia-Ryan RA, LaRocca TJ, Sindler AL, Zigler MC, Murphy MP, Seals DR.** Mitochondria-targeted antioxidant (MitoQ) ameliorates age-related arterial endothelial dysfunction in mice. *J Physiol* 592: 2549–2561, 2014.
37. **Hagmar M, Eriksson MJ, Lindholm C, Schenck-Gustafsson K, Hirschberg AL.** Endothelial function in post-menopausal former elite athletes. *Clin J Sport Med* 16: 247–252, 2006.
38. **Hayashi K, Miyagawa K, Sato K, Ueda R, Dohi Y.** Temocapril, an angiotensin converting enzyme inhibitor, ameliorates age-related increase in carotid arterial stiffness in normotensive subjects. *Cardiology* 106: 190–194, 2006.
39. **Hayashi K, Sugawara J, Komine H, Maeda S, Yokoi T.** Effects of aerobic exercise training on the stiffness of central and peripheral arteries in middle-aged sedentary men. *Jpn J Physiol* 55: 235–239, 2005.

40. **Heffernan KS, Chale A, Hau C, Cloutier GJ, Phillips EM, Warner P, Nickerson H, Reid KF, Kuvin JT, Fielding RA.** Systemic vascular function is associated with muscular power in older adults. *J Aging Res* 2012: 386387, 2012.
41. **Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, Ezekowitz MD, Finkelstein EA, Hong Y, Johnston SC, Khera A, Lloyd-Jones DM, Nelson SA, Nichol G, Orenstein D, Wilson PW, Woo YJ; American Heart Association Advocacy Coordinating Committee; Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Arteriosclerosis; Thrombosis and Vascular Biology; Council on Cardiopulmonary; Critical Care; Perioperative and Resuscitation; Council on Cardiovascular Nursing; Council on the Kidney in Cardiovascular Disease; Council on Cardiovascular Surgery and Anesthesia, and Interdisciplinary Council on Quality of Care and Outcomes Research.** Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. *Circulation* 123: 933–944, 2011.
42. **Herrera MD, Mingorance C, Rodriguez-Rodriguez R, Alvarez de Sotomayor M.** Endothelial dysfunction and aging: an update. *Ageing Res Rev* 9: 142–152, 2010.
43. **Jablonski KL, Chonchol M, Pierce GL, Walker AE, Seals DR.** 25-Hydroxyvitamin D deficiency is associated with inflammation-linked vascular endothelial dysfunction in middle-aged and older adults. *Hypertension* 57: 63–69, 2011.
44. **Jablonski KL, Fedorova OV, Racine ML, Geolfos CJ, Gates PE, Chonchol M, Fleenor BS, Lakatta EG, Bagrov AY, Seals DR.** Dietary sodium restriction and association with urinary marinobufagenin, blood pressure, and aortic stiffness. *Clin J Am Soc Nephrol* 8: 1952–1959, 2013.
45. **Jablonski KL, Gates PE, Pierce GL, Seals DR.** Low dietary sodium intake is associated with enhanced vascular endothelial function in middle-aged and older adults with elevated systolic blood pressure. *Ther Adv Cardiovasc Dis* 3: 347–356, 2009.
46. **Jablonski KL, Racine ML, Geolfos CJ, Gates PE, Chonchol M, McQueen MB, Seals DR.** Dietary sodium restriction reverses vascular endothelial dysfunction in middle-aged/older adults with moderately elevated systolic blood pressure. *J Am Coll Cardiol* 61: 335–343, 2013.
47. **Kaplon RE, Chung E, Reese L, Cox-York K, Seals DR, Gentile CL.** Activation of the unfolded protein response in vascular endothelial cells of nondiabetic obese adults. *J Clin Endocrinol Metab* 98: E1505–E1509, 2013.
48. **Kelly R, Hayward C, Avolio A, O'Rourke M.** Noninvasive determination of age-related changes in the human arterial pulse. *Circulation* 80: 1652–1659, 1989.
49. **Klonizakis M, Alkhatib A, Middleton G, Smith MF.** Mediterranean diet- and exercise-induced improvement in age-dependent vascular activity. *Clin Sci (Lond)* 124: 579–587, 2013.
50. **Lakatta EG, Levy D.** Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: part I: aging arteries: a "set up" for vascular disease. *Circulation* 107: 139–146, 2003.
51. **Lakatta EG, Levy D.** Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part II: the aging heart in health: links to heart disease. *Circulation* 107: 346–354, 2003.
52. **LaRocca TJ, Henson GD, Thorburn A, Sindler AL, Pierce GL, Seals DR.** Translational evidence that impaired autophagy contributes to arterial ageing. *J Physiol* 590: 3305–3316, 2012.
53. **Laurent P, Marenco P, Castagna O, Smulyan H, Blacher J, Safar ME.** Differences in central systolic blood pressure and aortic stiffness between aerobically trained and sedentary individuals. *J Am Soc Hypertens* 5: 85–93, 2011.
54. **Lesniewski LA, Connell ML, Durrant JR, Folian BJ, Anderson MC, Donato AJ, Seals DR.** B6D2F1 mice are a suitable model of oxidative stress-mediated impaired endothelium-dependent dilation with aging. *J Gerontol A Biol Sci Med Sci* 64: 9–20, 2009.
55. **Lesniewski LA, Durrant JR, Connell ML, Henson GD, Black AD, Donato AJ, Seals DR.** Aerobic exercise reverses arterial inflammation with aging in mice. *Am J Physiol Heart Circ Physiol* 301: H1025–H1032, 2011.
56. **Lesniewski LA, Zigler ML, Durrant JR, Nowlan MJ, Folian BJ, Donato AJ, Seals DR.** Aging compounds western diet-associated large artery endothelial dysfunction in mice: prevention by voluntary aerobic exercise. *Exp Gerontol* 48: 1218–1225, 2013.
57. **London GM, Pannier B.** Arterial functions: how to interpret the complex physiology. *Nephrol Dial Transplant* 25: 3815–3823, 2010.
58. **Lonn E, Bosch J, Teo KK, Pais P, Xavier D, Yusuf S.** The polypill in the prevention of cardiovascular diseases: key concepts, current status, challenges, and future directions. *Circulation* 122: 2078–2088, 2010.
59. **Lunder M, Janic M, Jug B, Sabovic M.** The effects of low-dose fluvastatin and valsartan combination on arterial function: a randomized clinical trial. *Eur J Intern Med* 23: 261–266, 2012.
60. **McCall DO, McGartland CP, McKinley MC, Patterson CC, Sharpe P, McCance DR, Young IS, Woodside JV.** Dietary intake of fruits and vegetables improves microvascular function in hypertensive subjects in a dose-dependent manner. *Circulation* 119: 2153–2160, 2009.
61. **McEniery CM, Wallace S, Mackenzie IS, McDonnell B, Yasmin Newby DE, Cockcroft JR, Wilkinson IB.** Endothelial function is associated with pulse pressure, pulse wave velocity, and augmentation index in healthy humans. *Hypertension* 48: 602–608, 2006.
62. **Mitchell GF.** Arterial stiffness and hypertension. *Hypertension* 64: 13–18, 2014.
63. **Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, Vita JA, Levy D, Benjamin EJ.** Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation* 121: 505–511, 2010.
64. **Mitchell GF, Izzo JL Jr, Lacourciere Y, Ouellet JP, Neutel J, Qian C, Kerwin LJ, Block AJ, Pfeffer MA.** Omapatrilat reduces pulse pressure and proximal aortic stiffness in patients with systolic hypertension: results of the conduit hemodynamics of omapatrilat international research study. *Circulation* 105: 2955–2961, 2002.
65. **Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, Vasan RS, Levy D.** Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. *Hypertension* 43: 1239–1245, 2004.
66. **Miyachi M, Donato AJ, Yamamoto K, Takahashi K, Gates PE, Moreau KL, Tanaka H.** Greater age-related reductions in central arterial compliance in resistance-trained men. *Hypertension* 41: 130–135, 2003.
67. **Molmen-Hansen HE, Stolen T, Tjonna AE, Aamot IL, Ekeberg IS, Tyldum GA, Wisloff U, Ingul CB, Stoylen A.** Aerobic interval training reduces blood pressure and improves myocardial function in hypertensive patients. *Eur J Prevent Cardiol* 19: 151–160, 2012.
68. **Mora S, Cook N, Buring JE, Ridker PM, Lee IM.** Physical activity and reduced risk of cardiovascular events: potential mediating mechanisms. *Circulation* 116: 2110–2118, 2007.
69. **Moreau KL, Donato AJ, Seals DR, DeSouza CA, Tanaka H.** Regular exercise, hormone replacement therapy and the age-related decline in carotid arterial compliance in healthy women. *Cardiovasc Res* 57: 861–868, 2003.
70. **Moreau KL, Gavin KM, Plum AE, Seals DR.** Oxidative stress explains differences in large elastic artery compliance between sedentary and habitually exercising postmenopausal women. *Menopause* 13: 951–958, 2006.
71. **Moreau KL, Stauffer BL, Kohrt WM, Seals DR.** Essential role of estrogen for improvements in vascular endothelial function with endurance exercise in postmenopausal women. *J Clin Endocrinol Metab* 98: 4507–4515, 2013.
72. **Muller-Delp JM, Spier SA, Ramsey MW, Delp MD.** Aging impairs endothelium-dependent vasodilation in rat skeletal muscle arterioles. *Am J Physiol Heart Circ Physiol* 283: H1662–H1672, 2002.
73. **Nichols WW, Denardo SJ, Wilkinson IB, McEniery CM, Cockcroft J, O'Rourke MF.** Effects of arterial stiffness, pulse wave velocity, and wave reflections on the central aortic pressure waveform. *J Clin Hypertens* 10: 295–303, 2008.
74. **Nosaka T, Tanaka H, Watanabe I, Sato M, Matsuda M.** Influence of regular exercise on age-related changes in arterial elasticity: mechanistic insights from wall compositions in rat aorta. *Can J Appl Physiol* 28: 204–212, 2003.
75. **Nualnim N, Barnes JN, Tarumi T, Renzi CP, Tanaka H.** Comparison of central artery elasticity in swimmers, runners, and the sedentary. *Am J Cardiol* 107: 783–787, 2011.
76. **Nualnim N, Parkhurst K, Dhindsa M, Tarumi T, Vavrek J, Tanaka H.** Effects of swimming training on blood pressure and vascular function in adults >50 years of age. *Am J Cardiol* 109: 1005–1010, 2012.
77. **O'Rourke MF, Safar ME.** Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. *Hypertension* 46: 200–204, 2005.

78. **Paul V, Ekambaram P.** Involvement of nitric oxide in learning & memory processes. *Indian J Med Res* 133: 471–478, 2011.
79. **Pearson KJ, Baur JA, Lewis KN, Peshkin L, Price NL, Labinskyy N, Swindell WR, Kamara D, Minor RK, Perez E, Jamieson HA, Zhang Y, Dunn SR, Sharma K, Pleshko N, Woollett LA, Csiszar A, Ikeno Y, Le Couteur D, Elliott PJ, Becker KG, Navas P, Ingram DK, Wolf NS, Ungvari Z, Sinclair DA, de Cabo R.** Resveratrol delays age-related deterioration and mimics transcriptional aspects of dietary restriction without extending life span. *Cell Metab* 8: 157–168, 2008.
80. **Pierce G, Eskurza I, Walker A, Fay T, Seals D.** Sex-specific effects of habitual aerobic exercise on brachial artery flow-mediated dilation in middle-aged and older adults. *Clin Sci (Lond)* 120: 13–23, 2011.
81. **Pierce GL, Beske SD, Lawson BR, Southall KL, Benay FJ, Donato AJ, Seals DR.** Weight loss alone improves conduit and resistance artery endothelial function in young and older overweight/obese adults. *Hypertension* 52: 72–79, 2008.
82. **Pierce GL, Donato AJ, LaRocca TJ, Eskurza I, Silver AE, Seals DR.** Habitually exercising older men do not demonstrate age-associated vascular endothelial oxidative stress. *Aging Cell* 10: 1032–1037, 2011.
83. **Pierce GL, Eskurza I, Walker AE, Fay TN, Seals DR.** Sex-specific effects of habitual aerobic exercise on brachial artery flow-mediated dilation in middle-aged and older adults. *Clin Sci (Lond)* 120: 13–23, 2011.
84. **Rammos C, Hendgen-Cotta UB, Sobierajski J, Bernard A, Kelm M, Rassaf T.** Dietary nitrate reverses vascular dysfunction in older adults with moderately increased cardiovascular risk. *J Am Coll Cardiol* 63: 1584–1585, 2014.
85. **Rippe C, Lesniewski L, Connell M, LaRocca T, Donato A, Seals D.** Short-term calorie restriction reverses vascular endothelial dysfunction in old mice by increasing nitric oxide and reducing oxidative stress. *Aging Cell* 9: 304–312, 2010.
86. **Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Dai S, de Simone G, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Greenlund KJ, Hailpern SM, Heit JA, Ho PM, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, McDermott MM, Meigs JB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Rosamond WD, Sorlie PD, Stafford RS, Turan TN, Turner MB, Wong ND, Wylie-Rosett J; American Heart Association Statistics Committee and Stroke Statistics Subcommittee.** Heart disease and stroke statistics–2011 update: a report from the American Heart Association. *Circulation* 123: e18–e209, 2011.
87. **Ros E, Hu FB.** Consumption of plant seeds and cardiovascular health: epidemiological and clinical trial evidence. *Circulation* 128: 553–565, 2013.
88. **Salminen A, Hyttinen JM, Kauppinen A, Kaarniranta K.** Context-dependent regulation of autophagy by IKK-NF-κB signaling: impact on the aging process. *Int J Cell Biol* 2012: 849541, 2012.
89. **Sandoo A, van Zanten JJ, Metsios GS, Carroll D, Kitas GD.** The endothelium and its role in regulating vascular tone. *Open Cardiovasc Med J* 4: 302–312, 2010.
90. **Schaun MI, Dipp T, Rossato Jda S, Wilhelm EN, Pinto R, Rech A, Plentz RD, Homem de Bittencourt PI, Reischak-Oliveira A.** The effects of periodized concurrent and aerobic training on oxidative stress parameters, endothelial function and immune response in sedentary male individuals of middle age. *Cell Biochem Funct* 29: 534–542, 2011.
91. **Seals DR.** Edward F. Adolph Distinguished Lecture: the remarkable anti-aging effects of aerobic exercise on systemic arteries. *J Appl Physiol* 117: 425–439, 2014.
92. **Seals DR, Desouza CA, Donato AJ, Tanaka H.** Habitual exercise and arterial aging. *J Appl Physiol* 105: 1323–1332, 2008.
93. **Seals DR, Jablonski KL, Donato AJ.** Aging and vascular endothelial function in humans. *Clin Sci (Lond)* 120: 357–375, 2011.
94. **Seals DR, Kaplon RE, Gioscia-Ryan RA, LaRocca TJ.** You're only as old as your arteries: translational strategies for preserving vascular endothelial function with aging. *Physiology (Bethesda)* 29: 250–264, 2014.
95. **Seals DR, Walker AE, Pierce GL, Lesniewski LA.** Habitual exercise and vascular ageing. *J Physiol* 587: 5541–5549, 2009.
96. **Sindler AL, Fleenor BS, Calvert JW, Marshall KD, Zigler ML, Lefer DJ, Seals DR.** Nitrite supplementation reverses vascular endothelial dysfunction and large elastic artery stiffness with aging. *Aging Cell* 10: 429–437, 2011.
97. **Soucy KG, Ryoo S, Benjo A, Lim HK, Gupta G, Sohi JS, Elser J, Aon MA, Nyhan D, Shoukas AA, Berkowitz DE.** Impaired shear stress-induced nitric oxide production through decreased NOS phosphorylation contributes to age-related vascular stiffness. *J Appl Physiol* 101: 1751–1759, 2006.
98. **Stanimirovic DB, Friedman A.** Pathophysiology of the neurovascular unit: disease cause or consequence? *J Cereb Blood Flow Metab* 32: 1207–1221, 2012.
99. **Sugawara J, Akazawa N, Miyaki A, Choi Y, Tanabe Y, Imai T, Maeda S.** Effect of endurance exercise training and curcumin intake on central arterial hemodynamics in postmenopausal women: pilot study. *Am J Hypertens* 25: 651–656, 2012.
100. **Swift DL, Earnest CP, Blair SN, Church TS.** The effect of different doses of aerobic exercise training on endothelial function in postmenopausal women with elevated blood pressure: results from the DREW study. *Br J Sports Med* 46: 753–758, 2012.
101. **Swift DL, Weltman JY, Patrie JT, Saliba SA, Gaesser GA, Barrett EJ, Weltman A.** Predictors of improvement in endothelial function after exercise training in a diverse sample of postmenopausal women. *J Womens Health (Larchmt)* 23: 260–266, 2014.
102. **Taddei S, Galetta F, Virdis A, Ghiadoni L, Salvetti G, Franzoni F, Giusti C, Salvetti A.** Physical activity prevents age-related impairment in nitric oxide availability in elderly athletes. *Circulation* 101: 2896–2901, 2000.
103. **Taddei S, Virdis A, Ghiadoni L, Mattei P, Sudano I, Bernini G, Pinto S, Salvetti A.** Menopause is associated with endothelial dysfunction in women. *Hypertension* 28: 576–582, 1996.
104. **Taddei S, Virdis A, Ghiadoni L, Salvetti G, Bernini G, Magagna A, Salvetti A.** Age-related reduction of NO availability and oxidative stress in humans. *Hypertension* 38: 274–279, 2001.
105. **Taddei S, Virdis A, Ghiadoni L, Salvetti G, Bernini G, Magagna A, Salvetti A.** Age-related reduction of NO availability and oxidative stress in humans. *Hypertension* 38: 274–279, 2001.
106. **Taddei S, Virdis A, Mattei P, Ghiadoni L, Gennari A, Fasolo CB, Sudano I, Salvetti A.** Aging and endothelial function in normotensive subjects and patients with essential hypertension. *Circulation* 91: 1981–1987, 1995.
107. **Tanaka H, DeSouza CA, Seals DR.** Absence of age-related increase in central arterial stiffness in physically active women. *Arterioscler Thromb Vasc Biol* 18: 127–132, 1998.
108. **Tanaka H, Dinenno FA, Monahan KD, Clevenger CM, DeSouza CA, Seals DR.** Aging, habitual exercise, and dynamic arterial compliance. *Circulation* 102: 1270–1275, 2000.
109. **Thijssen DH, Rongen GA, van Dijk A, Smits P, Hopman MT.** Enhanced endothelin-1-mediated leg vascular tone in healthy older subjects. *J Appl Physiol* 103: 852–857, 2007.
110. **Timmerman KL, Volpi E.** Endothelial function and the regulation of muscle protein anabolism in older adults. *Nutr Metab Cardiovasc Dis* 23, Suppl 1: S44–S50, 2013.
110a. **United States Census Bureau**. *Population Projections. Table 12. Projections of the Population by Age and Sex for the United States 2010 to 2050*. (online) http://www.census.gov/population/projections/data/national/2008/summarytables.html [3 November 2014].
111. **Vaitkevicius PV, Fleg JL, Engel JH, O'Connor FC, Wright JG, Lakatta LE, Yin FC, Lakatta EG.** Effects of age and aerobic capacity on arterial stiffness in healthy adults. *Circulation* 88: 1456–1462, 1993.
112. **Virdis A, Ghiadoni L, Giannarelli C, Taddei S.** Endothelial dysfunction and vascular disease in later life. *Maturitas* 67: 20–24, 2010.
113. **Vita JA, Keaney JF Jr.** Endothelial function: a barometer for cardiovascular risk? *Circulation* 106: 640–642, 2002.
114. **Vlachopoulos C, Dima I, Aznaouridis K, Vasiliadou C, Ioakeimidis N, Aggeli C, Toutouza M, Stefanadis C.** Acute systemic inflammation increases arterial stiffness and decreases wave reflections in healthy individuals. *Circulation* 112: 2193–2200, 2005.
115. **Walker AE, Eskurza I, Pierce GL, Gates PE, Seals DR.** Modulation of vascular endothelial function by low-density lipoprotein cholesterol with aging: influence of habitual exercise. *Am J Hypertens* 22: 250–256, 2009.
116. **Walker AE, Kaplon RE, Pierce GL, Nowlan MJ, Seals DR.** Prevention of age-related endothelial dysfunction by habitual aerobic exercise in healthy humans: possible role of nuclear factor-κB. *Clin Sci (Lond)* 127: 645–654, 2014.
117. **Wang M, Zhang J, Jiang LQ, Spinetti G, Pintus G, Monticone R, Kolodgie FD, Virmani R, Lakatta EG.** Proinflammatory profile within the grossly normal aged human aortic wall. *Hypertension* 50: 219–227, 2007.

118. **Wang Y, Rimm EB, Stampfer MJ, Willett WC, Hu FB.** Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. *Am J Clin Nutr* 81: 555–563, 2005.
119. **Welsch MA, Dobrosielski DA, Arce-Esquivel AA, Wood RH, Ravussin E, Rowley C, Jazwinski SM.** The association between flow-mediated dilation and physical function in older men. *Med Sci Sports Exerc* 40: 1237–1243, 2008.
120. **Werner TJ, Boutagy NE, Osterberg KL, Rivero JM, Davy KP.** Singular and combined effects of nebivolol and lifestyle modification on large artery stiffness in hypertensive adults. *Ther Adv Cardiovasc Dis* 7: 285–292, 2013.
121. **Widlansky ME, Gokce N, Keaney JF Jr, Vita JA.** The clinical implications of endothelial dysfunction. *J Am Coll Cardiol* 42: 1149–1160, 2003.
122. **Wohlfahrt P, Somers VK, Cifkova R, Filipovsky J, Seidlerova J, Krajcoviechova A, Sochor O, Kullo IJ, Lopez-Jimenez F.** Relationship between measures of central and general adiposity with aortic stiffness in the general population. *Atherosclerosis* 235: 625–631, 2014.
123. **Wong RH, Berry NM, Coates AM, Buckley JD, Bryan J, Kunz I, Howe PR.** Chronic resveratrol consumption improves brachial flow-mediated dilatation in healthy obese adults. *J Hypertens* 31: 1819–1827, 2013.
124. **Yoshizawa M, Maeda S, Miyaki A, Misono M, Choi Y, Shimojo N, Ajisaka R, Tanaka H.** Additive beneficial effects of lactotripeptides intake with regular exercise on endothelium-dependent dilatation in postmenopausal women. *Am J Hypertens* 23: 368–372, 2010.
125. **Yoshizawa M, Maeda S, Miyaki A, Misono M, Saito Y, Tanabe K, Kuno S, Ajisaka R.** Effect of 12 weeks of moderate-intensity resistance training on arterial stiffness: a randomised controlled trial in women aged 32–59 years. *Br J Sports Med* 43: 615–618, 2009.
126. **Zanetti M, Gortan Cappellari G, Burekovic I, Barazzoni R, Stebel M, Guarnieri G.** Caloric restriction improves endothelial dysfunction during vascular aging: effects on nitric oxide synthase isoforms and oxidative stress in rat aorta. *Exp Gerontol* 45: 848–855, 2010.
127. **Zhang C, Rexrode KM, van Dam RM, Li TY, Hu FB.** Abdominal obesity and the risk of all-cause, cardiovascular, and cancer mortality: sixteen years of follow-up in U.S. women. *Circulation* 117: 1658–1667, 2008.