habitual exercise and arterial aging

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WE HAVE KNOWN THAT AGING IS associated with changes in the function and structure of arteries since the late 1800s (84). Although of interest to physiologists, early observations were not of major biomedical importance because of the low prevalence of cardiovascular diseases (CVD) at the time. Today, CVD is the leading cause of morbidity and mortality in modern societies, and this is largely attributable to disorders of the arteries (4). Advancing age is a major risk factor for CVD and appears to exert its pathological influence primarily via adverse effects on arteries (54). Thus human aging is associated with arterial dysfunction and an increased risk of clinical vascular disease.

In contrast to age, regularly performed physical exercise in general, and aerobic exercise/fitness in particular, are associated with enhanced vascular function and reduced risk of CVD (7, 35, 99). The influence of regular resistance exercise (i.e., strength training, weight lifting, etc.) on arteries and CVD is less clear. However, the importance of resistance training in preserving strength suggests that it can play a significant role in the maintenance of functional capacity with aging. Taken together, these observations suggest that habitual exercise may exert its beneficial effects on physiological function and risk of CVD with aging at least in part by minimizing or preventing adverse changes in the structure and function of arteries.

This brief review will focus on the modulatory influence of regular exercise on selective changes in arterial function and structure with aging that we have studied over the last decade, especially large elastic artery stiffness and vascular endothelial function. Because of the larger amount of data available, the effects of aerobic exercise will be discussed in some detail. The influence of resistance exercise and combined aerobic and resistance training will be described where information exists. We will emphasize the results of investigations performed on healthy adult humans, using findings obtained in experimental animals and patients with CVD to extend insight into the underlying cellular and molecular mechanisms. Detailed descriptions of methodology and the integrative physiological mechanisms mediating arterial aging are available in the original research articles cited and the other brief reviews in this series. A discussion of aerobic training and age-associated changes in active muscle blood flow during acute exercise is available elsewhere (80, 119).

LARGE ELASTIC ARTERY STIFFNESS

A number of methodologies have been used to assess the elastic properties of arteries in humans. Pulse wave velocity (PWV) has
been most frequently used as a measure of arterial stiffness (105, 113). Augmentation index, an index of wave reflection that can be influenced by arterial stiffness, also has been employed (105, 113). Arterial compliance has been measured by simultaneous application of ultrasound imaging and applanation tonometry (67, 106).

Changes with Age

Stiffening of large elastic arteries (e.g., aorta and carotid artery) with aging was originally documented by Charles Roy in 1881 (84) and became the basis for William Osler’s famous saying that “man is as old as his arteries” (76). Based on cross-sectional observations, large elastic artery stiffness is progressively greater (compliance is lower) with advancing age even in healthy groups of men and women (5, 105, 113). We find 40–50% differences in large elastic artery stiffness and compliance between ~age 25 and 75 yr in healthy adults without clinical disease or major coronary risk factors (67, 106). Based on aortic PWV, increases in large elastic artery stiffness with age appear to be similar in men and women (61, 94). In contrast to large elastic arteries, peripheral arteries do not obviously stiffen with aging in healthy humans (67, 105, 106).

Changes in the composition of the arterial wall, including fragmentation of elastin and increases in collagen deposition, collagen cross-linking (associated with greater accumulation of advanced glycation end products), interstitial cell adhesion molecules, and growth factors, as well as vascular smooth muscle cell hypertrophy, are believed to be important mechanisms in mediating arterial stiffness with aging (53, 74). Functional changes that result in increased vascular smooth muscle tone such as increased sympathetic nervous system activity and bioactivity of locally synthesized vasoconstrictor molecules (e.g., endothelin-1) and reduced endothelial dilator production (111), perhaps linked to oxidative stress (70), also likely contribute. Arterial stiffening with aging does not appear to depend on the presence of atherosclerosis because it is observed in rural Chinese populations who have a low prevalence of atherosclerotic diseases (5), in rigorously screened healthy men and women (67, 106), and in animal species resistant to the development of atherosclerosis (36, 83).

Influence of Habitual Exercise

The initial clue that habitual aerobic exercise might attenuate age-associated increases in large elastic artery stiffness was an observation from the Baltimore Longitudinal Study of Aging that older male endurance athletes demonstrated lower aortic PWV, augmentation index and systolic blood pressure than their sedentary peers (113). We subsequently found that aortic PWV, augmentation index, and 24-h systolic and pulse pressure were greater in postmenopausal compared with premenopausal sedentary, but not endurance exercise-trained, healthy women (90, 105). Results of follow-up investigations showed that age-associated reductions in carotid artery compliance were only ~50% as great in healthy men and women who performed habitual aerobic exercise compared with sedentary adults (67, 106) (Fig. 1). Daily brisk walking for ~3 mo improved carotid artery compliance in previously sedentary middle-aged/older men (106) (Fig. 1) and postmenopausal women (69) to levels observed in age-matched endurance exercise-trained adults, suggesting that even moderate aerobic exercise may produce an optimal effect.

There are limited data as to the mechanisms mediating these favorable modulatory effects of habitual aerobic exercise. One possibility is that regular exercise minimizes or reverses age-related structural changes in the arterial wall. This may contribute in settings of prolonged exercise training; however, there are no data available to support this mechanism. Reduced stiffness with aging in exercise-trained rodents is not dependent on structural changes in elastin and collagen (74). Functional adaptations may be involved, especially in response to shorter term exercise training (67, 106). Expression of genes associated with local vasodilatory signaling are modified in aorta of exercise-trained rats (60). Moreover, ascorbic acid (vitamin C) improves carotid artery compliance in sedentary, but not endurance exercise-trained postmenopausal women (70), suggesting reduced oxidative stress in the habitually exercising state. Improvements in carotid artery compliance in response to regular moderate-intensity exercise are independent of baseline compliance and changes in conventional risk factors for CVD, body composition, and aerobic fitness (67, 106).

In contrast to findings on healthy middle-aged and older men and women, regular aerobic exercise may not improve arterial stiffness in certain groups of adults with chronically elevated arterial blood pressure (32, 91). Moreover, higher intensity resistance exercise training is associated with greater rather than lower large elastic artery stiffness in young and middle-aged adults (6, 62), although the addition of aerobic exercise may counteract this negative influence (50). Moderate-intensity resistance exercise training does not influence arte-
rrial stiffness in healthy young men (82) or postmenopausal women (10).

**VASCULAR ENDOTHELIAL FUNCTION**

**Endothelium-Dependent Dilation**

Endothelium-Dependent Dilation (EDD) has been assessed primarily using two models: increases in forearm blood flow to intra-brachial artery infusions of endothelial dilators like acetylcholine (20) and brachial artery flow-mediated dilation (12). The former examines resistance vessel EDD in response to a pharmacological stimulus, whereas the latter model assesses large conduit artery EDD in response to the physiological stimulus of increased shear stress.

**Changes with age.** Both expressions of EDD demonstrate reductions with age, even in healthy sedentary adults, although the temporal pattern of decline may differ (11, 103). The decrease in EDD may be delayed to an older age in women than men, possibly because of menopause-associated estrogen deficiency (11, 103). In contrast to EDD, endothelium-independent dilation is not reduced with aging in healthy adults (11, 103).

In humans, the age-associated decline in EDD is mediated in part by an oxidative stress-dependent reduction in nitric oxide (NO) production and bioavailability (27, 30, 101). Based on data from experimental animals, the reduction in EDD is not consistently associated with reductions in the expression or activity of endothelial NO synthase (eNOS) (95, 115), the enzyme responsible for endothelial production of NO. Rather, superoxide reaction with NO and oxidation of tetrahydrobiopterin (BH4), the key cofactor for NO synthesis, production of reactive oxygen species (ROS), and expression of the oxidant-producing enzyme, NADPH oxidase, in the mammary artery (1) may contribute to impaired EDD with aging (96, 102). Other mechanisms discussed in this highlighted series include inflammation, arginase, and p66Shc signaling (9, 14, 86).

**Influence of habitual exercise.** EDD is greater in middle-aged and older men who regularly perform aerobic exercise compared with their sedentary peers (17, 30, 100), and it is similar to (17, 30) or modestly lower than (100) that of young healthy sedentary and exercising men (Fig. 2). Three months of moderate-intensity aerobic exercise training improves EDD in previously sedentary middle-aged and older healthy men (17) (Fig. 2) and in patients with the metabolic syndrome but no clinical disease (58). It is unknown whether aerobic exercise training is associated with enhanced EDD with aging in women, although EDD is increased after a single bout of aerobic exercise in postmenopausal, but not premenopausal, women (41). Aerobic exercise training improves EDD in middle-aged and older patients with CVD (38), but consistent effects have not been observed in healthy young men and women with normal baseline function (13, 17, 51, 65). Moderate-intensity resistance exercise training has no obvious effect on EDD in healthy postmenopausal women (10).

The greater EDD in middle-aged and older men who regularly perform aerobic exercise is mediated in part by increased NO bioavailability (100). Tonic NO production also appears to be enhanced in these men (100) (Fig. 3), as well as in previously sedentary middle-aged and older men who walk for 12 wk (Fig. 3). Aerobic training-induced improvements in EDD and NO bioavailability are associated with an increase in eNOS gene and protein expression in older rats (95) and an increase in eNOS protein and serine 1177 phosphorylation of eNOS in patients with coronary artery disease (37), but no information is available on healthy older humans. The production and bioactivity of other endothelial-derived vasodilators such as prostacyclin also are increased with aerobic exercise training in older animals (96).

The greater NO-mediated improvements in EDD in middle-aged and older adults who perform aerobic exercise may be secondary to reduced oxidative stress. Acute administration of supraphysiological concentrations of antioxidants (vitamin C) improves EDD in sedentary, but not in endurance exercise-trained, men (30, 100). Habitually exercising middle-aged and older adults have lower malondialdehyde and higher total oxyradical scavenging capacity compared with age-matched sedentary adults, and this is related to enhanced EDD (34). In patients with coronary disease, aerobic exercise training is associated with decreased production of reactive oxygen species and expression of the oxidant-producing enzyme, NADPH oxidase, in the mammary artery (1). That acute BH4 administration restores EDD in older sedentary adults without affecting...
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Endothelial Fibrinolytic Capacity

The hemostatic mechanism responsible for the proteolytic degradation of intravascular fibrin is the fibrinolytic system. This enzymatic pathway maintains vascular patency by converting the inactive proenzyme plasminogen to the active enzyme, plasmin, which lyases fibrin into soluble degradation products (77). The vascular endothelium plays a prominent role in modulating fibrinolytic system function through its synthesis and release of tissue-type plasminogen activator (t-PA), the primary plasminogen activator, and its biological inhibitor plasminogen activator inhibitor-1 (PAI-1) (59). t-PA is the key enzyme involved in initiating an endogenous fibrinolytic response as a result of its ability to preferentially activate plasminogen on the surface of developing thrombi (29). The capacity of the endothelium to rapidly release t-PA from intracellular storage pools, rather than circulating plasma concentrations, determines the efficacy of endogenous fibrinolysis (78, 114).

t-PA is released by endothelial cells in response to a variety of stimuli including thrombin, hypoxia, and inflammatory cytokines (77, 104). Endothelial agonists such as substance P, bradykinin and methacholine also stimulate the release of t-PA in a dose-dependent fashion. The use of these vasoactive agents at subsystemic, locally active concentrations in the forearm coupled with measures of blood flow and arterial-

venous differences in t-PA provide a reproducible method for directly assessing the rate of t-PA release from the endothelium in vivo (8, 49, 93).

Changes with age. The capacity of the endothelium to release t-PA declines with age in healthy sedentary men as indicated by a marked reduction in endothelial t-PA release across the forearm vasculature in response to bradykinin (93). The underlying mechanisms are unknown. Data from animal models suggest that t-PA expression may decline with age, resulting in reduced intracellular bioavailability (2, 79). Increased oxidative stress also may be a contributing factor (116). Indeed, oxygen free radicals inhibit t-PA release from endothelial cells (92). In contrast to men, endothelial t-PA release does not differ in healthy sedentary premenopausal and postmenopausal women (45, 46), and it is greater in middle-aged and older women compared with men of similar age (97).

Influence of habitual exercise. In contrast to their healthy sedentary peers, aerobic exercise-trained men do not demonstrate an age-related decline in the capacity of the endothelium to release t-PA (93) (Fig. 4). Consistent with this, 12 wk of moderate-intensity aerobic exercise training (daily walking) improves endothelial t-PA release in previously sedentary middle-aged and older men to levels of young men, independent of changes in body composition, CVD risk factors and maximal exercise capacity (93) (Fig. 4). There is no information regarding the effects of habitual resistance exercise on endothelial t-PA release.

The mechanisms mediating the beneficial effects of regular aerobic exercise on endothelial t-PA release with aging in healthy men have not been established. In cultured endothelial cells, shear stress induces t-PA transcription and protein synthesis (18, 19). Exercise-training associated increases in cytoplasmic calcium levels may potentiate t-PA release (56). Reduced oxidative stress also could contribute, although no data are available to support this possibility.

Endothelial Progenitor Cells

Currently there are no clear, consensus criteria for identifying bone marrow-derived circulating endothelial progenitor cells (EPC). Nevertheless, EPC are believed to play a critical role in maintaining, repairing, and regenerating the vascular endothelial monolayer and restoring functional activity (22, 28, 112). Reduced number and impaired function of EPC are associated with endothelial dysfunction (43, 73) and increased risk and severity of CVD (43, 88).

Fig. 3. Reductions in FBF in response to intra-brachial artery infusion of Nω-monomethyl L-arginine (L-NMMA) (i.e., tonic nitric oxide release) in sedentary (left) and endurance exercise-trained (middle) healthy young and middle-aged/older men, and before and after an aerobic exercise intervention in middle-aged/older men (right). *P < 0.05.

EDD in their exercising peers suggests that the lower oxidative stress-related increase in NO bioavailability in older adults who exercise may be linked to reduced oxidation and enhanced bioactivity of BH4 (31).

Exercise-induced increases in shear stress as a result of increased blood flow and pulse pressure to both active and nonactive limbs are thought to be important stimuli for the molecular endothelial adaptations to aerobic training because improvements in EDD are observed in arteries outside the exercising limbs (35, 52, 109). Increases in EDD in response to an aerobic exercise intervention are not dependent on improvements in conventional risk factors for CVD and are not related to increases in maximal aerobic exercise capacity (17).

Endothelial Fibrinolytic Capacity

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Changes with age. Aging is associated with reduced number and function of circulating EPCs (21, 42, 47, 87, 110). EPC colony-forming capacity and migratory activity decline with age even in healthy men (42, 47), and they are related to both reductions in EDD and increased Framingham risk score (42, 43). EPC colony formation and migration are greater in middle-aged and older women compared with men (44), suggesting that EPC function may be better preserved with aging in women.

Influence of habitual exercise. In patients with cardiovascular risk factors and CVD, aerobic exercise intervention increases EPC number (55, 85, 98), and this is strongly related to improvements in EDD (98). Increases in both EPC colony-forming and migratory capacity are observed after 12 wk of brisk walking in the absence of changes in body composition, CVD risk factors, and maximal exercise capacity in previously sedentary healthy middle-aged and/or older men (47), although unchanged EPC number also has been reported after endurance training (110). In general, these findings support the idea that increases in EPC number and function may contribute to improvements in vascular endothelial function with regular aerobic exercise in middle-aged and older adults.

ARTERIAL WALL THICKNESS

Changes with Age

The intima-media wall thickness (IMT) of the carotid and femoral arteries are independent predictors of future CVD (75), and both increase with age even in healthy men and women (68, 72, 89, 107). The increases in IMT are mediated by thickening of both the intimal and medial layers (81, 117). In healthy adults, these age-associated changes likely reflect arterial remodeling in response to intravascular hemodynamic changes related in part to increases in local arterial blood pressure (107). Lumen diameter also widens as part of this remodeling (54, 107). In patients with major risk factors or clinical CVD, increased IMT also may reflect atherosclerotic plaques (118).

Influence of Habitual Exercise

Early cross-sectional studies using questionnaires to assess habitual physical activity reported lower, not different and even greater carotid IMT in physically active compared with sedentary adults (15, 33). In rigorously screened healthy men and women in whom maximal aerobic exercise capacity is objectively assessed, the age-associated increase in carotid IMT does not differ among sedentary, moderately active, and endurance exercise-trained adults (68, 108). In agreement with these cross-sectional observations, carotid IMT is unaffected by 3 mo of daily walking (68, 108). Similar findings have been reported for resistance exercise training (62, 63). The absence of habitual exercise effects may be explained by the fact that carotid artery pressure, a strong independent predictor of carotid IMT in healthy adults (107), is not associated with exercise status (62, 63, 68, 108). Carotid lumen diameter does not differ with age among groups differing in exercise behavior, nor does it change in response to aerobic or resistance exercise interventions (62, 63, 68, 108).

In contrast to carotid IMT, femoral IMT is smaller in both moderately active and endurance exercise-trained compared with sedentary healthy middle-aged and older adults, and the age-associated increases in femoral IMT are smaller in exercising than in sedentary adults (25, 68). Femoral artery IMT is reduced after 12 wk of daily walking in middle-aged and older men in the absence of changes in CVD risk factors (25). The greatest modulatory effects of habitual aerobic exercise on femoral IMT are observed in older adults (72). Habitual exercise also is associated with greater femoral lumen diameter (25, 68). Together, these changes may reflect expansive arterial remodeling to normalize wall stress in response to increases in femoral blood flow evoked by daily aerobic leg exercise (25). They are not related to changes in the aerobic exercise stimulus, exercise capacity or CVD risk factors (25). Femoral IMT is not affected by resistance exercise training (3, 64).

PERIPHERAL VASOCONSTRICTION (REDUCTIONS IN BASAL LEG BLOOD FLOW)

Changes with Age

Basal leg blood flow decreases linearly between the ages of 25 and 65 yr in healthy men (24, 48, 64) and is 25–30% lower in postmenopausal compared with premenopausal healthy women (66, 69). These age-associated reductions in blood flow are mediated by corresponding decreases in vascular conductance (23, 24, 48, 64, 66, 69). These changes are most closely

Fig. 4. Net release rate of tissue-type plasminogen activator (t-PA) antigen across the forearm in response to intrabrachial artery infusion of bradykinin in sedentary (left) and endurance exercise-trained (middle) healthy young and middle-aged/older men, and before and after an aerobic exercise intervention in middle-aged/older men (right). *P < 0.05. [From Smith et al. (93).]
related to decreases in estimated leg oxygen consumption, but they are not completely explained by reductions in leg fat-free mass, i.e., blood flow per kg fat-free mass decreases with age (23, 26, 69). In men, the reductions in leg blood flow and vascular conductance with age are mediated by increased sympathetic α-adrenergic tone (26), perhaps linked to increased oxidative stress (48), whereas the latter appears to play a significant but lesser role in women (71).

**Influence of Habitual Exercise**

Despite the apparent mechanistic role for oxidative stress and evidence that regular aerobic exercise is associated with reduced vascular oxidative stress, reductions in basal leg blood flow and vascular conductance with age are similar in healthy sedentary, moderately active, and endurance exercise-trained men (24, 25). In contrast, reductions in basal leg blood flow and vascular conductance are not observed in middle-aged compared with young resistance exercise-trained men, independent of leg fat-free mass (64). Consistent with this, 13 wk of resistance exercise that has no effect on leg fat-free mass or cardiac output restores basal leg blood flow in healthy middle-aged and older adults (3). Thus resistance exercise training may be associated with preserved basal whole-leg blood flow with aging.

**SUMMARY AND CONCLUSIONS**

The influence of habitual aerobic and resistance exercise on arterial aging is summarized in Fig. 5. Regular aerobic exercise is associated with smaller increases in arterial stiffness with aging and improves stiffness in previously sedentary middle-aged and older healthy men and women. Reduced oxidative stress may contribute to these effects, but little insight is available as to mechanisms of action. Higher, but not moderate, intensity resistance exercise may exert a negative influence on arterial stiffness when performed without aerobic training.

Habitual aerobic exercise acts to preserve several vascular endothelial functions that decline with age, and it can restore lost function in older adults, although definitive data only are available on men. Reduced oxidative stress and, in the case of EDD, greater NO bioavailability associated with increased eNOS expression/activation and BH4 bioactivity, may be involved, but more mechanistic insight is needed.

Carotid IMT is not affected by chronic exercise status, but femoral IMT is smaller in aerobic exercise-trained adults across age, probably as part of expansive arterial remodeling in response to acute exercise-related changes in intravascular wall stress. Resistance, but not aerobic, exercise training may preserve and restore basal whole leg blood flow with aging.

Collectively, these findings support the view that regular physical activity, particularly large-muscle aerobic exercise, is an effective strategy for combating several adverse physiological changes associated with arterial aging, especially increases in large-elastic artery stiffness and vascular endothelial dysfunction. This modulatory influence may explain in part why physically active and aerobically fit middle-aged and older adults have increased cardiovascular functional capacity and a lower prevalence of CVD than sedentary adults.

**FUTURE DIRECTIONS**

There is extensive need for both applied/clinical and basic research on this topic. Because regular resistance exercise is now recognized as a fundamental strategy for maintenance of muscle strength with advancing age, a much better understanding is needed of how this type of training, alone and combined with complementary aerobic and perhaps other forms of physical exercise, affects the function and structure of arteries as we age. A practical, but important issue is the volume and intensity of exercise required to minimize arterial aging, and whether this is function-specific. For example, our work indicates that 12 wk of brisk walking can restore EDD in some middle-aged and older adults, but it did not restore carotid artery compliance (17, 106). Little is known about the efficacy of habitual exercise for treating vascular dysfunction in adults over 70–80 yr of age and those with clinical CVD or risk factors for CVD. In some cases (e.g., aging, aerobic exercise and EDD), no data are available on women. Moreover, in clinical practice exercise is not prescribed in isolation but rather with other lifestyle (e.g., weight loss; low-fat diet; smoking cessation) and pharmacological strategies. Does exercise exert additive or synergistic effects with other treatments or is there redundancy? Cross-sectional (comparison of sedentary and exercise-trained adults), exercise intervention, and longitudinal (following sedentary and exercising adults over time) studies all can be used.

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**Fig. 5. Summary of modulatory effects of habitual aerobic and resistance exercise on selective features of arterial aging in healthy adults.** –, inhibition of; +, exacerbation of; ↔, no influence on the effects of sedentary aging; ?, no published data available; EDD, endothelium-dependent dilation; t-PA, tissue-type plasminogen activator (fibrinolytic capacity); EPC, endothelial progenitor cells; IMT, intima-media thickness; BF, blood flow; VC, vascular conductance.
to provide insight. In particular, more information is needed as to the effects of aging and habitual exercise on EPC-mediated (or assisted) vascular repair.

Presently, we have some understanding, albeit incomplete, of the integrative (whole artery to molecular) physiological mechanisms underlying the effects of regular aerobic exercise on EDD with aging. In comparison, very little is known about the mechanisms by which habitual exercise influences arterial stiffness and other functions as we age. The main limitation with human investigations is a lack of access to internal (nonperipheral) arteries for tissue sampling and manipulation of signaling pathways, particularly in healthy adults. In vivo and in vitro animal and vascular cell models, as well as innovative methods in humans, will be needed to pursue these issues. Mechanisms previously implicated in age- and CVD-related physiological dysfunction represent potential targets as to how exercise may impact arterial aging. A major candidate in this context is inflammation, including its interaction with oxidative stress. The roles played by exercise-induced changes in the bioactivity of novel signaling molecules and the transcriptional and posttranscriptional regulation of the genes involved in mediating functional improvements represent important goals of future research in this area.

CLINICAL SIGNIFICANCE

As the populations in the United States and other modern societies age, greater resources will be required to meet health care needs. The associated costs and demand pose a real and increasingly imminent threat to our health care systems. A key strategy will be delaying the onset and development of age-associated physiological dysfunction and disease. Habitual exercise, combined with other lifestyle and pharmacological interventions, can be a powerful tool to achieve this goal. Along with cancer, CVDs are the leading cause of morbidity and premature mortality in industrialized nations. Much of the etiology of CVD is attributable to disorders of the arteries. As such, the use of regular exercise to delay, slow and, in some cases, prevent the development of arterial dysfunction and disease can play a key role in promoting healthy aging.

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