



Published in final edited form as:

Physiology (Bethesda). 2011 June ; 26(3): 132–145. doi:10.1152/physiol.00052.2010.

Vascular Effects of Exercise: Endothelial Adaptations Beyond Active Muscle Beds

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Abstract

Endothelial adaptations to exercise training are not exclusively conferred within the active muscle beds. Herein, we summarize key studies that have evaluated the impact of chronic exercise on the endothelium of vasculatures perfusing nonworking skeletal muscle, brain, viscera, and skin, concluding with discussion of potential mechanisms driving these endothelial adaptations.

The beneficial effects of physical activity and exercise training in prevention and treatment of cardiovascular disease are not entirely mediated by the reduction of systemic risk factors (71, 100, 141, 195). Indeed, current data suggest that at least 40% of the cardiovascular risk reduction associated with exercise cannot be accounted for by the modification of established or emerging risk factors (71, 100, 141, 195). In view of this risk reduction gap, it is likely that exercise exerts direct effects on the vascular wall of arteries, a concept recently referred to as vascular conditioning (65, 71, 195). The vascular effects of chronic exercise may include structural (angiogenesis and remodeling) and functional adaptations, the latter involving phenotypic alterations of vascular smooth muscle and endothelial cells. Of particular interest is the possible direct impact of physical activity on sustaining or restoring a normal/healthy endothelial phenotype (65, 69, 93, 114, 115, 127, 144, 195). In fact, it is this favorable effect of exercise on the endothelium that may explain, at least in part, the well established association between physical activity and reduced cardiovascular events and mortality (11, 149, 155, 162, 207).

During exercise, the metabolic demands of contracting muscle cause vasodilation and increased blood flow in the working muscle tissue. As a result, it is believed that shear stress is elevated in the vasculatures supplying blood to the active cardiac and skeletal muscle (116). It is commonly accepted that repeated episodes of elevated shear stress represent the primary physiological signal for endothelial adaptations to exercise training (65, 69, 93, 114, 116, 127, 195). The concept that vascular adaptations are mediated by shear stress-dependent mechanisms is indeed supported by cell and organ culture (18, 21, 22, 40, 171, 180) as well as in vivo animal (117, 133) and human (67, 78, 148, 198) experiments. For example, data from rats (117, 133) suggest that exercise training-induced adaptations in skeletal muscle arteries are related to muscle fiber type and recruitment patterns. That is, exercise-induced vascular adaptations occur, spatially, in the area of muscle tissue with the

greatest relative increase in fiber activity and presumably shear stress during exercise training bouts. Moreover, recent data in humans (198) indicate that brachial artery endothelial adaptations to handgrip exercise training can be abolished when the increases in conduit artery shear associated with each bout of handgrip exercise are experimentally prevented.

Intriguingly, however, adaptations to exercise training have also been observed in vasculatures perfusing tissues that do not exhibit increased metabolism during exercise and that, as a result, are exposed to a lesser elevation in blood flow (or no increase at all) (109–111, 212). These data suggest the possibility that regular exercise may also exert a nonspecific, systemic effect on endothelial function/phenotype and that such effects may partially occur through shear stress-independent mechanisms. However, it should be noted that, even in the absence of increased mean shear stress, changes in shear profiles (i.e., waveforms) occur (63, 64, 66, 181, 194), and therefore the role of shear stress as a systemic modulator of endothelial health with exercise training cannot be ruled out.

Several reviews (65, 69, 93, 114, 115, 127, 144, 195) have described the vascular effects of exercise training in the coronary and skeletal muscle circulations and a debate remains on whether these adaptations extend to regions less active during exercise bouts (70, 192). In this regard, although previous reports have suggested the presence of a systemic influence of exercise on the vasculature (69, 70, 72, 93, 195), we are unaware of a review exclusively focused on endothelial adaptations in blood vessels of tissues beyond the active muscle beds. Therefore, the main purpose of the present review is to examine those key studies that have evaluated the impact of chronic exercise on the endothelium in noncontracting tissues. Specifically, we describe whether endothelial adaptations occur with exercise training in vasculatures of various tissues that have smaller increases (or no increase) in activity (“inactive”) during exercise and identify or speculate whether these vessels are exposed to changes in shear stress during bouts of physical activity. Furthermore, based on this information, a hypothesis is formulated regarding alternative signals (i.e., circumferential stretch, circulating humoral factors) that may act independently or synergistically with shear forces in the modulation of systemic endothelial adaptations to chronic exercise.

Effects of Exercise Training on the Endothelium of Noncontracting Tissues

“Inactive” Skeletal Muscle Circulation

Important evidence endorsing the concept that exercise training exerts systemic effects on the arterial endothelium derives from human studies evaluating endothelial function in arteries that perfuse limbs that would be considered nonworking during training bouts (70, 192). Many, although not all (45, 53, 61, 105, 143, 161, 190, 191), interventional studies have demonstrated that lower-limb exercise training (e.g., cycling or walking) is associated with vascular adaptations in the arms (28, 46, 62, 85, 103, 118, 122, 124–126, 164, 197, 202, 203, 205, 206). Such vascular adaptations in the upper limbs occur even when subjects are instructed to not grip the handle bars or railings (124–126, 202, 203, 205, 206) to minimize arm activity during exercise bouts. Remarkably, the favorable chronic effects of exercise training in the nonworking limbs are manifested in both the conduit arteries (i.e., brachial and radial) (28, 118, 122, 124, 164, 197, 202, 203, 205, 206) as well as resistance arteries (46, 62, 85, 103, 125, 126). In these studies, conduit artery endothelial adaptations have been examined non-invasively via flow-mediated dilation, whereas resistance vessel endothelial adaptations have typically been assayed by measuring forearm blood flow responses to intrabrachial artery infusions of endothelium-dependent vasodilators such as acetylcholine (ACh).

Given that 50–80% of resting forearm blood flow is directed to the skeletal muscle (36), the exercise training-mediated increase in forearm vascular responsiveness to intrabrachial artery ACh infusion has been interpreted as evidence of endothelial adaptation in the nonworking skeletal muscle vasculature. However, it should be noted that intra-arterial infusions of ACh has also been shown to increase skin blood flow, although the precise distribution of changes in limb conductance during ACh infusion is not known (54, 178). In light of the evidence that exercise training improves endothelial responsiveness to local (intra-arterial) administration of ACh in the skin (10) (see *Cutaneous Circulation* section), it is possible that increases in whole forearm blood flow responses to ACh following exercise training may be explained, at least in part, by endothelial adaptations conferred within the cutaneous circulation. Therefore, further research is necessary to dissect out what portion of the increase in forearm vascular responsiveness to ACh associated with lower-limb exercise training is reflective of endothelial adaptations within the noncontracting skeletal muscle.

There is evidence from animal studies supporting the concept that exercise training induces adaptations in the endothelium of vessels perfusing nonworking skeletal muscle. Studies in rats (109–111, 212) demonstrate that exercise training produces vascular changes in skeletal muscles (i.e., spinotrapezius) that exhibit no increase in metabolic activity or blood flow during treadmill exercise (146). For example, Lash et al. (111) demonstrated that 16 wk of exercise training increases ACh-induced vasodilation in arterioles of spinotrapezius muscle of healthy rats. These results have been confirmed by Xiang and colleagues (212) examining the effect of exercise training in lean and obese Zucker rats. They found that 4–5 wk of exercise improved ACh-induced vasodilation in spinotrapezius arterioles in both groups of rats, with the greatest effect found in the obese animals (212). The trend for a greater improvement of endothelial function in disease states is also supported by human studies (69, 127, 144, 195). In this regard, available literature makes it apparent that the beneficial effects of leg exercise on endothelial function of resistance arteries and conduit arteries of nonworking human limbs are most notable in subject populations with preexisting cardiovascular risk factors or disease; that is, in individuals with compromised basal vascular function (69, 127, 144, 195). It is plausible that there is an interaction between endothelial health and exercise training such that the endothelium is more amenable to exercise when impairment or disease is present (93, 127, 144, 154).

The mechanisms by which endothelial adaptations are manifested in the nonworking arms of individuals undergoing leg training have not been fully elucidated. During the last decade, research has focused on examining changes in blood flow and shear rate magnitude and patterns in the upper limbs as potential signals for adaptations to training. It is now established that, at the onset of lower-limb dynamic exercise (i.e., first ~10 min), the brachial artery is exposed to a marked increase in retrograde and oscillatory shear (63, 64, 66, 181, 194) likely as a result of the increase in downstream resistance (181). As exercise continues, blood flow to the forearm is increased and primarily directed to the skin to serve thermoregulatory needs (97, 152) (see *Cutaneous Circulation*). Cutaneous vasodilation (and the subsequent decrease in forearm vascular resistance) observed during prolonged exercise results in a significant augmentation of shear stress in the upstream conduit arteries (i.e., brachial and radial) (153, 181, 188, 196) and the partial removal of the initial increase in retrograde and oscillatory shear (181) (FIGURE 1). These observations stimulate the hypothesis that the favorable vascular adaptations occurring in the conduit arteries feeding the nonworking limbs (28, 118, 122, 124, 164, 197, 202, 203, 205, 206) may be mediated by the same signal through which conduit arteries perfusing the active limbs are believed to adapt; that is, repeated bouts of elevated shear stress (65, 69, 116, 127, 195, 198). Green and coworkers (196) recently addressed this premise using an acute exercise paradigm. They bilaterally evaluated brachial artery endothelium-dependent dilation before and after a 30-min bout of cycling exercise. In one arm, the increase in brachial artery shear rate during

exercise was prevented by the application of a forearm cuff at 60 mmHg. The authors found that brachial artery vasomotor function was improved after cycling exercise in the uncuffed, but not cuffed, arm (196), hence suggesting that a single episode of increased shear at the conduit artery of the nonworking limb produces endothelial adaptations. Recent data from the same group further support the argument that shear stress is capable of inducing conduit artery adaptations in humans even when the hyperemic stimulus is independent of exercise (i.e., local heating) (148).

In summary, extensive evidence in rodents indicates that exercise training induces favorable endothelial adaptations in arteries of nonworking skeletal muscle, whereas evidence in humans support that these adaptations occur in nonworking limbs that contain muscles not involved in the exercise bout. In humans, the mechanisms for conduit artery vascular adaptations may be attributed to elevated shear stress (induced by an increase in blood flow directed to the skin), whereas the mechanisms responsible for adaptations in non-recruited skeletal muscle resistance arteries remain unclear. It is plausible that, during exercise, the marked sympathetically mediated arteriolar vasoconstriction in the nonworking skeletal muscle may result in actual increases in shear, which in turn may act as a signal to the endothelium.

Cerebral Circulation

It is well established that regular physical activity is associated with reduced cerebrovascular events (e.g., stroke) (119, 120, 128, 174, 208). Although the mechanisms responsible for these vasoprotective effects of exercise are largely unknown, it is reasonable to propose that exercise may exert its beneficial effects on the cerebral circulation by reducing carotid plaque burden and instability, hence decreasing the risk of emboli. There is a large body of evidence indicating that exercise training improves endothelial function (52) and decreases arterial stiffness (57, 177, 187) in the carotid artery. In addition, although less compelling, there is also evidence that physical activity is associated with reduced carotid artery intima-media thickness (101, 136, 201), an index of pre-clinical atherosclerosis. Importantly, exercise training has been shown to alter composition of carotid artery plaque and reduce its vulnerability to rupture (166). Furthermore, there is also evidence that exercise training exerts direct protective effects on the cerebral circulation. Gertz et al. (60) reported that, 4 wk after brain ischemia, mice that exercise trained exhibited increased resting cerebral blood flow in the ischemic lesion as well as better functional and cognitive outcomes. Importantly, the protective effects of physical activity were abolished in animals either co-treated with a NOS inhibitor or in animals lacking eNOS gene expression (eNOS^{-/-}) (60). Similarly, Endres et al. (55) demonstrated that 3 wk of exercise training led to an increase in resting cerebral blood flow and a reduction of cerebral infarct size in wild-type, but not eNOS^{-/-}, mice. Together, these data unequivocally demonstrate that eNOS upregulation is critical in enhancing postischemic recovery of cerebral function and increasing cerebral collateral flow and/or cerebral resistance to ischemia. Studies in rats also indicate that protein expression and endothelium-dependent vasodilation of cerebral arteries and arterioles can be modulated with exercise training. Mayhan et al. found that 6–10 wk of exercise training increased eNOS protein expression and NO-dependent dilation in the basilar artery (132) and cerebral (pial) arterioles (130) in diabetic rats. The same group of investigators evaluated the influence of exercise training on reversing the deleterious effects of cigarette smoking in the cerebral circulation (131). They found that exercise training restored adenosine-induced vasodilation in cerebral (pial) arterioles in nicotine-treated rats, whereas no effects of exercise were observed in healthy control (untreated) rats (131). Furthermore, the increase in superoxide ion production associated with the chronic exposure to nicotine was reduced by exercise training, possibly as a result of an increase in SOD-1 protein expression (131). Recently, in a large cross-sectional study ($n = 307$), Ainslie et al. (1) provided evidence in

humans that resting blood flow velocity in the middle cerebral artery is elevated by habitual exercise across different ages, independent of possible confounding variables. It is possible that increases in cerebral blood flow associated with training (1) are mediated, at least in part, by local changes within the vasculature. The observation that habitual physical activity increases resting cerebral blood flow velocity is in contrast to the consistent finding that exercise training does not alter resting muscle blood flow (8, 68, 129, 156, 200). We speculate this incongruence between vascular beds may be explained by regional differences in basal sympathetic tone following exercise training. In this regard, recent data suggest that the skeletal muscle and cerebral circulations are differentially regulated by the sympathetic nervous system during acute exercise (81).

It is important to emphasize that exercise training-induced vascular adaptations in the cerebral circulation are accompanied by improvements in functional and cognitive outcomes as well (94). Indeed, results of longitudinal studies indicate that exercise training can provide a positive effect on human cognitive abilities (106), potentially counteracting declines in cerebral tissue density (33) and increasing brain volume in aging humans (34). Recent data from the Framingham Heart Study indicates that decreasing cardiac function, even at normal cardiac index levels, is associated with accelerated brain aging (95). Of note, there is growing evidence that cerebrovascular dysfunction plays a role not only in vascular causes of cognitive impairment but also in Alzheimer's disease (89). In fact, novel data implies that there may be a causal link between endothelium-derived NO deficiency and Alzheimer's disease (27).

Although the mechanisms by which regular physical activity induces beneficial effects in the cerebral vasculature have not been entirely elucidated, it is possible that repeated exposure to increases in blood flow and shear stress in specific regions of the brain during exercise plays a role. Indeed, there is consistent evidence that blood flow is increased in some areas of the brain during physical activity (55, 58, 82–84, 90, 98, 99, 142, 151). Blood flow is primarily directed to those areas that are intensely activated during exercise (e.g., motor and sensory cortex, and cerebellum-cerebral cortex) (56). Interestingly, the increase in cerebral blood flow appears to be related to the intensity of the activity up to ~60% of $\text{VO}_{2\text{max}}$, an intensity after which flow decreases toward baseline levels (83, 142). The increase in cerebral blood flow seems to be linked to the local vasodilator action of metabolites and/or perhaps to other local effects produced by increased neural activity during exercise (113, 150, 167, 182), whereas the limitation of hyperemia above 60% of $\text{VO}_{2\text{max}}$ may result from decreased arterial PCO_2 (13).

In summary, the studies presented herein provide evidence that exercise training is able to promote favorable adaptations in the cerebral vasculature, blood vessels which are not viewed as belonging to exercising tissue. The signals mediating these adaptations are unclear at this time, but the increase in shear stress associated with regional increases in cerebral blood flow during acute exercise should be considered as a prime candidate.

Splanchnic and Renal Circulations

Blood flow to the splanchnic and renal vasculatures is markedly reduced during dynamic exercise as a function of exercise intensity (2, 73, 76, 86, 160, 173, 213). Data from animal and human studies suggest that exercise training results in an attenuated reduction of blood flow to both the splanchnic and renal vasculatures at a given absolute exercise intensity (3, 30, 147, 163, 173). Rowell et al. (173) first described this effect on total splanchnic flow in humans via measures of indocyanine green clearance before and after training. More recent animal studies have demonstrated that the attenuated reduction of splanchnic blood flow after training occurs in most, if not all, splanchnic vasculatures (3, 47, 147). The training-induced adaptations in the splanchnic and renal vasculature may be sensitive to the type of

training since adaptations in the renal arteries has been reported following endurance treadmill training but not following high-intensity interval sprint training in rats (147).

The training-induced attenuation of splanchnic and renal vasoconstriction during exercise is likely mediated by both local and systemic adaptations. Centrally, exercise training-induced reductions in peripheral sympathetic outflow, which mediates visceral constriction during exercise, likely accounts for a large part of the attenuated splanchnic and renal vasoconstriction during exercise after training (5, 31, 47, 77, 87, 145, 165, 176, 193). Indeed, endurance training and daily exercise reduce renal sympathetic nerve activity during exercise due, in part, to enhanced cardiac baroreflex inhibition of sympathetic outflow to the mesenteric and renal circulation in rabbits (47, 48). Additionally, local adaptations within the vascular wall also appear to contribute to the training-induced attenuation of visceral constriction during exercise. Most, but not all (134, 186), *in vitro* studies examining the splanchnic and renal vasculature have revealed enhanced ACh-induced vasodilation and reduced vasoconstriction to various agonists (nor-epinephrine, phenylephrine, prostaglandin F_{2α}, KCl) related, at least in part, to enhanced production of and/or sensitivity to endogenous endothelial dilators (i.e., nitric oxide, prostacyclin, etc.) (4, 19, 20, 25, 42, 43, 74, 92, 112, 214). Mechanistically, the training-induced enhancement of mesenteric vasodilation to ACh appears to be accounted for by an enhanced endothelium-derived hyperpolarizing factor-dependent component of ACh dilation and subsequent activation of calcium activated K⁺ channels (19, 214); however, other unexamined pathways may be involved as well. These adaptations have been reported in both conduit arteries and the microcirculation of the splanchnic and renal vasculatures (4, 19, 25, 43, 112, 134). Furthermore, similar training-induced changes in local vascular reactivity occur in both healthy and diseased animals (i.e., obesity, hypertension) (4, 19, 20, 25, 42, 43, 74, 92, 112, 214). Further research is necessary to determine the extent to which findings concerning training effects on visceral circulations from animal studies can be extrapolated to humans.

Taken together, these studies suggest that exercise training induces local vascular adaptations of the splanchnic and renal vasculatures that likely act to enhance nutrient absorption and utilization during exercise in the trained organism. Augmented cardiac output and mean arterial pressure during exercise coupled with visceral vasoconstriction (i.e., reduction in diameter) may lead to increases in shear stress despite the reduction of blood flow (160). Thus the signal for these chronic adaptations may be the repetitive bouts of increased shear stress occurring during acute exercise. However, the precise levels of shear stress present in the splanchnic and renal macro and microvasculatures during exercise have not been fully characterized.

Cutaneous Circulation

Endurance exercise training for a period of weeks to months results in cutaneous vascular adaptations characterized by increased endothelial-mediated vasomotor function. The main evidence for these adaptations derives from studies in which regional forearm skin blood flow responses were assessed during local administration of endothelium-dependent (ACh) and -independent (sodium nitroprusside) vasodilators or during local heating. For example, in a cross-sectional study, Kvernmo et al. (108) demonstrated that forearm skin blood flow responses to ACh were greater in elite endurance athletes than in control subjects who performed regular physical activity. In contrast, responses to sodium nitroprusside were not different between groups. Similarly, Roche et al. (172) recently reported an enhanced skin blood flow response to local heating in physically active children (aged 13–15 yr) compared with age-matched (less active) controls. Using a longitudinal study design, Wang (204) evaluated endothelium-dependent and -independent cutaneous vascular responses in sedentary but otherwise healthy males before and after 8 wk of exercise training. After completing the exercise training period, endothelium-dependent cutaneous vascular

responsiveness was increased, whereas endothelium-independent responses were unchanged. Interestingly, when subjects were then detrained for 8 wk, the training-mediated changes in vascular responsiveness were abolished (204). Similar detraining results have been shown when normally active subjects are confined to bedrest for 14–56 days (39, 44). Furthermore, it appears that regular exercise during bedrest prevents the decline in vascular responsiveness and maximal vasodilation in the skin (39, 44). Thus a number of studies and experimental models of increased and decreased physical activity support the notion that cutaneous vascular responsiveness, particularly to endothelium-dependent stimulation, is altered by physical activity. Increased physical activity is associated with increased cutaneous endothelial vasomotor responsiveness, whereas decreased physical activity is associated with decreased cutaneous vasomotor function.

It appears that the beneficial effects of exercise training on the cutaneous vascular endothelium are sufficient to stave off the progression toward microcirculatory dysfunction associated with aging and disease. Evidence for this comes from studies demonstrating that older individuals who exercise regularly have enhanced endothelial vasomotor function in the cutaneous circulation compared with their sedentary, age-matched counterparts (10). In fact, cutaneous microvascular endothelial function in physically active older persons is not different from that in recreationally active young individuals (10, 189). Similar effects of exercise on cutaneous microvascular function have been demonstrated in patients with Type 2 diabetes (32) and chronic venous disease (104). Thus it appears that regular exercise training increases cutaneous microvascular (endothelial) function in health and disease.

It is important to note that many of the studies discussed above (44, 104, 108, 189, 204) have examined the effect of physical activity/inactivity on microvascular function in the skin using iontophoretic application of ACh. Today, it is recognized that results obtained with this technique to test endothelial function of skin blood vessels must be interpreted cautiously (37, 38). Skin blood flow responses to ACh iontophoresis are only partly NO mediated and largely mediated by prostanoids (12, 51, 88). In addition, ACh iontophoresis induces an axon reflex that contributes to the increase in cutaneous blood flow (9). Nevertheless, Black et al. (10) used microdialysis for direct intradermal delivery of ACh to study chronic adaptations to exercise training and found similar effects to those reported by others (44, 104, 108, 189, 204).

The mechanisms responsible for the beneficial adaptations in the cutaneous vascular endothelium in response to exercise training have not been identified. The cutaneous circulation plays a pivotal role in the dissipation of heat during dynamic exercise, which is generated as the most abundant by-product of metabolism (96). As such, sevenfold increases in skin blood flow are not uncommon in subjects exercising at a moderate intensity in thermoneutral conditions (181) (FIGURE 1). In view of the cutaneous hyperemia associated with exercise, changes in hemodynamic forces are primary candidates for mechanisms through which beneficial adaptations are produced in response to exercise training. In this regard, a recent study by Green et al. (67) demonstrated that chronic forearm heating, which provides a similar hyperemic stimulus to that occurring during exercise, improves cutaneous microvascular vasodilator function. To investigate the mechanism of this beneficial effect, skin blood flow in one arm (but not the other) was manipulated by inflation of a proximal forearm cuff, resulting in significant attenuation of the forearm hyperemia during heating sessions. Interestingly, the arm in which hyperemia was blunted exhibited no adaptation to chronic heating, suggesting that repetitive increases in tissue perfusion are responsible for cutaneous vascular adaptations in this setting. Because changes in tissue perfusion are often related to changes in vascular wall shear stress, these results stimulate the possibility that shear stress signals endothelial adaptation in the cutaneous circulation and further suggest that increases in shear may be responsible for cutaneous vascular adaptations to exercise

training. However, it is currently unclear how changes in bulk blood flow during forearm heating (or exercise) translate to alterations in shear stress in the cutaneous microcirculation. Therefore, further investigation is necessary to clarify the role of hemodynamic forces in the cutaneous (endothelial) vascular adaptations resulting from chronic endurance exercise training.

Exercise-Induced Signals for Endothelial Adaptations in Noncontracting Tissues

Hemodynamic Forces

Although it is universally recognized that shear stress is a primary signal for exercise training-induced endothelial adaptations in active muscle beds, the literature summarized above appears to suggest that shear may also be a signal for endothelial adaptations in vasculatures perfusing noncontracting tissues. The concept that shear can signal the endothelium to alter its phenotype/function is well supported by in vitro (18, 21, 22, 40, 171, 180) and in vivo (15, 67, 138, 139, 196, 198) data and has been the subject of several reviews (21, 26, 40, 75, 116, 171). It is important to highlight that, during exercise, the signal triggering endothelial adaptations in blood vessels perfusing tissues outside actively contracting muscle may not only be increased mean shear stress but also the alteration in shear profiles (63, 64, 66, 181, 194) that result from hemodynamic changes (e.g., heart rate and pressure) during exercise. In this respect, Canty and Schwarz (16) demonstrated in conscious dogs that cardiac pacing at 200 beats/min produced a near doubling in coronary blood flow that resulted in epicardial artery dilation that was NO mediated. In contrast, a tripling in coronary blood flow induced by adenosine was equally effective in producing epicardial artery dilation; however, this dilation was not NO dependent. These observations suggest that alterations in the frequency of cyclic shear, and hence the profile of the shear waveform, may activate highly different signaling pathways than do increases in average shear stress. More research is warranted to isolate the influence of shear patterns from other exercise-related signals to fully evaluate the hypothesis that exercise-induced acute changes in shear waveforms modulate endothelial health systemically with training.

Several considerations should be taken into account when viewing the hypothesis that shear stress is an exercise-induced signal for endothelial adaptations in nonworking tissues. Shear stress ($4\eta\dot{Q}/\pi R^3$; where η = viscosity, \dot{Q} = blood flow, R = internal radius of the artery) is directly related to blood flow and viscosity but inversely related to arterial diameter. Accordingly, given that vascular tone (and hence diameter) is constantly regulated by central and local factors (e.g., shear stress), changes in blood flow through a given vessel do not always correspond with alterations in shear stress. In this regard, the extent to which enhanced blood flow or viscosity results in increased shear stress may be dependent on the caliber of the vessel and/or its ability to dilate in response to shear. Contrary to conduit arteries, given the remarkable capacity of arterioles to dilate and constrict, it is unclear to what degree changes in blood flow in the microvasculature translate into alterations in shear. As new in vivo imaging techniques emerge, future research should characterize the actual magnitudes and profiles of shear stress in the microcirculation during rest and exercise.

Importantly, shear stress may not be the only hemodynamic exercise-induced signal for systemic endothelial adaptations. Endothelial cells are also exposed to stress from distention of arteries caused by relaxation of smooth muscle in the wall or by increased transmural pressure across the arterial wall. Since endothelial cells are exposed to cyclic distention within each cardiac cycle and during exercise the frequency and magnitude of this distention is augmented, cyclic strain should be considered as a potential exercise-induced signal. In this regard, Awolesi et al. (6, 7) have shown that cyclic strain increases transcription of

eNOS in cultured endothelial cells. Similarly, it is demonstrated that distention of isolated arteries is a stimulus for increased expression of the eNOS gene (116, 209, 216). However, it is important to note that cyclic strain has also been associated with increased production of reactive oxygen species and expression of adhesion molecules including VCAM-1, ICAM-1, E-selectin, and MCP-1 (23, 24, 210, 211, 215). Although chronic exposure of endothelial cells to increased cyclic strain (as occurs with hypertension) may produce detrimental adaptations, based on the classical physiological concept of *hormesis*, it is plausible that recurring periods of exercise-induced cyclic strain and consequent oxidative stress may increase the tolerance of endothelial cells to withstand subsequent doses and hence stimulate a long-term protective effect. However, this is a hypothesis that needs to be tested. It is also possible that cyclic strain is most favorable to the endothelium when combined with increased shear stress. Interestingly, *in vitro* data suggest that changes in endothelial gene expression in response to shear stress and cyclic strain vary according to whether the two forces are applied separately or simultaneously (199).

Circulating Factors

In addition to evidence in the literature that exercise-induced adaptations of the endothelium result from increases in shear stress and/or cyclic strain (116), there is also growing evidence suggesting that changes in chemical signaling (i.e., hormones, cytokines, adipokines) may contribute to systemic benefits of chronic exercise on endothelial cells. Hemodynamic forces may interact with anti-atherogenic mediators such as insulin, adiponectin, and IL-6 and with inflammatory cytokines (pro-atherogenic mediators) in determination of endothelial cell phenotype/function. It appears that substances that signal remodeling and altered phenotype of endothelial and smooth muscle cells are also released in response to increased shear stress (80, 116, 121, 123).

With the acceptance that adipose tissue is an active metabolic organ that releases a growing number of adipokines (leptin, adiponectin, resistin, etc.) it seems reasonable to consider the hypothesis that chronic physical activity may have beneficial effects systemically on endothelial cell phenotype/function by modifying release of such adipokines from adipose tissue (17, 175). There is a growing consensus that the protective effect of exercise against vascular diseases may to some extent be ascribed to an anti-inflammatory effect of regular physical activity (157, 170). However, further research is required to fully evaluate the role of adipose tissue in the inflammatory processes generated in the peripheral circulation as well as the ability of exercise training to attenuate such vascular inflammation signaled from adipose tissue.

In this context, recent results indicate that exercise training alters gene expression in adipose tissue differently, i.e., has greater effects on some types of adipose tissue than others (35). Company et al. (35) recently examined the effects of exercise training on expression of 18 selected genes in the adipose tissue of pigs. These results indicated that exercise training had significant effects on expression of inflammatory cytokines and inflammatory mediators in epicardial and visceral adipose but not in subcutaneous adipose tissue (35). This, combined with observations that perivascular adipose tissue of normal pigs has an anti-contractile effect on coronary arteries, which is not apparent in the perivascular adipose tissue of pigs with advanced coronary artery disease (14, 169, 185), supports the following hypothesis: exercise training may restore/maintain normal phenotype of cells in adipose tissue resulting in a healthier adipokine release, thereby signaling optimal regulation of endothelial cell gene expression. Similar effects of perivascular adipose tissue may contribute to the beneficial influence of exercise training in non-coronary arteries as well.

In line with the acceptance of adipose tissue as an endocrine organ, Pedersen and colleagues (157, 158) have advocated that skeletal muscle should also be viewed as an endocrine organ.

In this regard, Pedersen et al. (157, 158) suggest that cytokines and other peptides that are produced, expressed, and released by muscle fibers and exert endocrine effects should be classified as “myokines.” The discovery that myokines are released during muscle contraction leads to the interesting hypothesis that the effect of regular physical activity on endothelial cell phenotype may be partially mediated by the repeated exposures of the endothelium to such circulating factors. The prototype myokine is IL-6 (157). During exercise, IL-6 is markedly increased in the circulation in both humans (79, 157–159) and animals (91) and precedes the appearance of other cytokines. IL-6 exerts favorable metabolic effects including fat oxidation and lipolysis in adipose tissue and furthermore augments insulin sensitivity in skeletal muscle (157). Importantly, there is evidence to support that IL-6 exerts anti-inflammatory effects by inducing production and release of anti-inflammatory cytokines, IL-10 and IL-1ra, and inhibiting TNF- α (157, 179, 183). Therefore, it is plausible that the release of IL-6 and/or other myokines from contracting muscle during exercise sets the stage for an anti-inflammatory environment that, over time, may contribute to the protective influence of habitual physical activity on vascular wall inflammation systemically.

Another putative signal for systemic endothelial adaptations that can be modulated with exercise training is insulin. There are numerous beneficial effects of insulin on endothelial cells, including the stimulation of endothelial-mediated vasodilation (184), increased production of NO (107), decreased production of reactive oxygen species (50), increased expression of antioxidant genes (59), and decreased expression of adhesion factors such as VCAM-1 (168). Conversely, loss of insulin signaling in endothelial cells accelerates atherosclerosis (168). Furthermore, although the systemic release of insulin is reduced during acute exercise bouts, it appears that chronic exercise is capable of increasing the sensitivity of endothelial vasomotor responses to insulin (137). These combined results support the hypothesis that exercise training may exert a systemic effect on endothelial phenotype and function in part through sensitizing the endothelium to the beneficial effects of insulin. Indeed, both insulin (at rest) and shear stress (during exercise) signal vasodilation in endothelial cells through the phospho-Akt/eNOS pathway; thus it is plausible that insulin and shear stress have synergistic effects on endothelial gene expression. That is, the effects of insulin on the endothelium may be enhanced following repeated exposures to increased shear stress.

The duration of exercise bouts generally ranges between 30 and 120 min. Therefore, the endothelium is likely exposed to increased shear stress and/or cyclic strain for a relatively short portion of a day (2–10% of 24 h). However, exercise may alter circulating factors beyond the duration of the exercise bout and therefore represent a significant stimulus to the vasculature. As work progresses in this area, we must consider the kinetics of these responses as well as the sequence of changes in endothelial gene expression following each exercise bout. This information will be important as we begin to establish signals responsible for changes in endothelial cell gene expression in the arteries feeding active muscle and those perfusing non-contracting tissues.

Summary

It is becoming increasingly recognized that endothelial adaptations to exercise training are not solely conferred within the active muscle beds. Indeed, herein, we have summarized evidence that regular physical activity can alter endothelial phenotype and function in vasculatures perfusing the nonworking skeletal muscle, brain, viscera, and skin. Although limited, there is also recent evidence that exercise training can alter the vasculature perfusing bone (49), adipose tissue (41), and male reproductive organs (29). Although the mechanisms driving exercise training-induced endothelial adaptations beyond the active

muscle beds are not established at this time, we propose hemodynamic forces (i.e., shear stress and cyclic strain) and/or circulating factors released from adipose tissue and skeletal muscle as likely signals responsible for the endothelial adaptations in these vasculatures (FIGURE 2). Given that localized exercise training (i.e., single arm or leg) does not exert systemic effects on the vasculature (102, 135, 140), it is possible that there is a threshold for hemodynamic forces and circulatory factors that may only be reached when exercise involves large muscle groups. Further research is warranted to shed light on our understanding of the exercise-mediated signals for endothelial adaptation and to determine how these signals synergistically interact in the systemic modulation of endothelial phenotype and function.

Acknowledgments

J. Padilla is supported by American Heart Association Grant 11POST5080002; G. H. Simmons is supported by National Institute of Arthritis and Musculoskeletal and Skin Diseases Grant T32-AR-048523; M. H. Laughlin is supported by National Heart, Lung, and Blood Institute Grants P01-HL-052490 and HL-36088.

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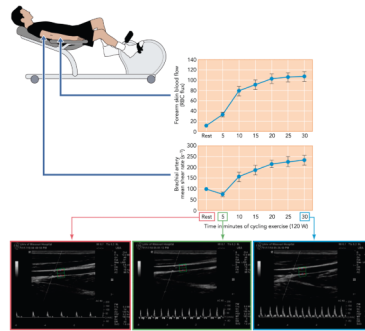


FIGURE 1. Forearm skin blood flow and brachial artery mean shear rate during prolonged cycling exercise

Increase in forearm skin blood flow and brachial artery mean shear rate during prolonged cycling exercise (*top* and *middle*) [data adapted from Simmons et al. (181)]. *Bottom*: original Doppler ultrasound images from a representative subject illustrate the remarkable changes in blood velocity profiles from rest (*left*) to early (*middle*) and prolonged (*right*) exercise.

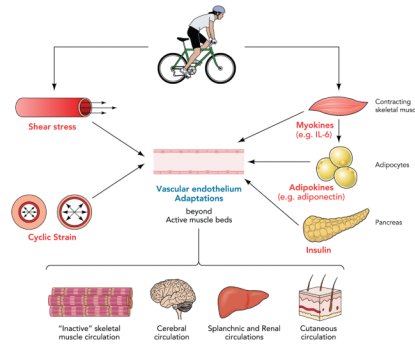


FIGURE 2. Summary of proposed mechanisms by which exercise training may alter endothelial cell phenotype and function beyond the active muscle beds

During a bout of exercise, endothelial gene expression can be regulated by changes in the magnitude and profiles of shear stress and cyclic strain as well as by circulating factors such as myokines released from contracting skeletal muscle. Exercise training may also restore/maintain normal phenotype of adipocytes resulting in a healthier adipokine release, thereby signaling expression of healthy endothelial cell genes. In addition, exercise training may exert a systemic effect on endothelial phenotype and function in part through sensitizing the endothelium to the beneficial effects of insulin.