Mechanism of Beneficial Effects of Physical Activity on Atherosclerosis and Coronary Heart Disease

Effects of exercise on endothelium and endothelium/smooth muscle cross talk: role of exercise-induced hemodynamics

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Newcomer SC, Thijssen DH, Green DJ. Effects of exercise on endothelium and endothelium/smooth muscle cross talk: role of exercise-induced hemodynamics. J Appl Physiol 111: 311–320, 2011. First published March 24, 2011; doi:10.1152/japplphysiol.00033.2011.—Physical activity, exercise training, and fitness are associated with decreased cardiovascular risk. In the context that a risk factor “gap” exists in the explanation for the beneficial effects of exercise on cardiovascular disease, it has recently been proposed that exercise generates hemodynamic stimuli which exert direct effects on the vasculature that are anti-atherogenic. In this review we briefly introduce some of the in vitro and in vivo evidence relating exercise hemodynamic modulation and vascular adaptation. In vitro data clearly demonstrate the importance of shear stress as a potential mechanism underlying vascular adaptations associated with exercise. Supporting this is in vivo human data demonstrating that exercise-mediated shear stress induces localized impacts on arterial function and diameter. Emerging evidence suggests that exercise-related changes in hemodynamic stimuli other than shear stress may also be associated with arterial remodeling. Taken together, in vitro and in vivo data strongly imply that hemodynamic influences combine to orchestrate a response to exercise and training that regulates wall stress and peripheral vascular resistance and contributes to the antiatherogenic impacts of physical activity, fitness, and training.

shear stress; cyclic stretch; oscillatory; exercise; hemodynamics

It is well established that increased levels of physical activity, exercise, and fitness decrease cardiovascular mortality (7, 8). However, the precise mechanisms underlying these beneficial effects remain unclear. Recent epidemiological data suggest that modifications in traditional and novel risk factors may account for <50% of the reduction in risk for coronary heart disease associated with exercise (78). The mechanisms underlying the remaining risk reduction have yet to be elucidated (32, 59, 78).

Recently, hemodynamic alterations that occur during exercise have been suggested to play a role in cardiovascular disease risk reduction (29, 32, 65). The underlying rationale is based on studies reporting an influence of hemodynamic profiles on conduit artery atherosclerotic susceptibility (122, 126). It follows that alterations in physiological variables that influence hemodynamic profiles (e.g., blood flow, pulse pressure, and muscle contraction) likely contribute to exercise-induced cardiovascular risk reduction by modifying the expression of genes that are linked to vascular health, function, and structure. The purpose of this review is to briefly introduce in vitro and in vivo experiments relating to exercise-mediated hemodynamic alterations and vascular adaptation.

Understanding Exercise-Induced Hemodynamic Effects on Vascular Gene Expression Through In Vitro Experimental Models

In vitro evidence for shear stress as a modulator of the exercise-induced changes to vascular phenotype. Exercise produces robust increases in blood flow to the heart and active skeletal muscle (2) (Fig. 1). These increases in blood flow during exercise generate shear forces that have been reported to alter gene expression in endothelial and vascular smooth muscle cells (65, 86, 118). Therefore, the beneficial effects of exercise on vascular health have often been attributed in the literature to exercise-induced increases in mean shear stresses
This is supported by data obtained from cell culture and isolated vessel preparations which demonstrate that increased shear stress positively modifies the expression of genes involved in the atherosclerotic process (84, 85, 91, 119, 123, 128). The impact that shear stress has on gene expression is highlighted by reports that increases in shear stress change the expression of ∼3,000 cultured endothelial cell genes as assessed by microarray analysis (50). The limited data obtained from in vivo models also support the notion that increases in mean shear stress provide a stimulus that is antiatherogenic. Specifically, increases in shear stress, produced by arteriovenous fistulas in rats and dogs, have been reported to increase mRNA, protein, and activity of endothelial nitric oxide synthase (eNOS) and decrease bioavailability of endothelin (ET-1) (75, 82).

While data linking increases in mean shear stress to atheroprotective changes in gene expression have focused attention on mean shear as a modulating stimulus, it is important to acknowledge that the beneficial effects of exercise on vascular health also occur in arteries that are not subjected to robust increases in mean shear stress during exercise (36, 72). This suggests that alterations in other hemodynamic stimuli, which occur during exercise, may also play a significant role in vascular health.

The pattern of the hemodynamic profile is also significantly altered when transitioning from rest to exercise (Fig. 1). During exercise the pattern of blood flow through the conduit arteries becomes more oscillatory in nature, resulting in both antegrade (forward) and retrograde (backward) components (36). Unlike unidirectional laminar shear, experiments utilizing cell culture and isolated vessel preparations suggest that some patterns of oscillatory shear produce a proatherogenic endothelial cell phenotype (10, 17, 26, 27, 53, 55, 73, 99, 128, 129). Specifically, oscillatory shear stress has been associated with decreased eNOS mRNA (26, 55, 99, 128, 129) and increased vascular cell adhesion molecule 1 (VCAM-1) mRNA, protein, and activity of endothelial nitric oxide synthase (eNOS) and decrease bioavailability of endothelin (ET-1) (10, 17, 26, 27, 53, 55, 73, 99, 128, 129). Specifically, oscillatory shear stress has been associated with decreased eNOS mRNA (26, 55, 99, 128, 129) and increased vascular cell adhesion molecule 1 (VCAM-1) mRNA, protein, and enzyme activity (4, 5). In contrast, other experiments reported that cyclic strain did not change eNOS mRNA expression in cultured endothelial cells (128, 129). The lack of changes in eNOS expression in addition to reported increases in MCP-1 (124), ICAM-1 (11, 12, 125), ET-1 (128), E-selectin (125) and reactive oxygen species (ROS) production (11, 124), suggests that cyclic strain likely produces a proatherogenic phenotype in cultured endothelial cells.

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Recent data obtained from an isolated vessel preparation suggests that reducing the cyclic strain stimulus decreases the phosphorylation of serine 1177 on eNOS and increases ROS production through the upregulation of p22-phox and p47-phox (106). The discrepancies in results obtained from endothelial cell culture and isolated whole vessel preparations cannot be accounted for by the presence of vascular smooth muscle in the later experimental paradigm, given that cyclic strain increases ROS production and muscle cell proliferation (43). Unfortunately, limited conclusions can be drawn from this study, as oscillatory shear stress was administered directly to the vascular smooth muscle cells, a scenario that does not occur in vivo in healthy arteries. Coculturing endothelial and vascular smooth muscle cells is a recent technique that has been developed to account for this limitation (47). Hastings et al. (47) reported that an oscillatory shear pattern was associated with an increase in VCAM-1 and a decrease in interleukin 8 (IL-8) and MCP-1 mRNA. Changes in vascular smooth muscle cell VCAM-1 mRNA were later reported to be modulated by IL-8 which was synthesized in the endothelial cells (46). These findings suggest that some oscillatory shear stress patterns may produce a proatherogenic vascular smooth muscle cell phenotype via endothelial cell-mediated mechanotransduction.

In vitro evidence for cyclic strain as a modulator of the exercise-induced changes to vascular phenotype. Increases in blood flow during exercise are also accompanied by significant increases in pulse pressure. This elevation in pressure across the cardiac cycle produces an increase in the rhythmic stretching (cyclic strain) of endothelial and vascular smooth muscle cells across the vasculature. The systemic nature of cyclic strain makes it an attractive mechanism for describing how exercise positively impacts vascular adaptation.

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MCP-1 in smooth muscle cell culture (42, 51). One might speculate that reported differences between data obtained in endothelial and smooth muscle cell culture vs. whole vessel preparations may reflect the necessary cross talk between endothelial and vascular smooth muscle cells in producing an antiatherogenic phenotype when exposed to a cyclic strain stimulus. Future research using cocultured endothelial and vascular smooth muscle cells will be required to determine if cross talk between endothelial and smooth muscle cells produces an antiatherogenic cell phenotype in response to cyclic strain.

In vitro evidence for shear stress and cyclic strain as a modulator of vascular structure. Enlargement of arterial vessels and collateralization likely contributes to the reductions in cardiovascular mortality associated with physical activity. It is not surprising then that hemodynamic stimuli have also been reported in the literature to play a significant role in the enlargement of existing arterial vessels (89). Specifically, increases in both radial wall and shear stresses have been attributed to exercise-induced increases in vascular caliber (89).

It is well established that arteries exposed to increases in shear stress outwardly remodel through nitric oxide-mediated pathways (94, 117). These findings suggest that increased shear stress can simultaneously serve as an antiatherogenic and arteriogenic stimulus. However, there is also evidence that proatherogenic hemodynamic stimuli may also be arteriogenic in nature (18, 48). For instance, increases in MCP-1, ICAM-1, and VCAM-1, that are associated with in vitro oscillatory shear and cyclic strain, have been reported to play a pivotal role in the initial stages of both arteriogenesis and atherogenesis (18, 48). This athero/arteriogenesis paradigm highlights the difficulty in classifying different hemodynamic stimuli that occur during exercise as good or bad relative to vascular health and emphasizes the strong links between structural remodeling and atherosclerosis.

Limitations of in vitro preparations. There are several limitations to drawing conclusions from data acquired from in vitro preparations regarding the impact of hemodynamic forces during exercise. The studies described above were not designed to determine whether exercise-mediated hemodynamic forces impact vascular health. The majority of these experiments investigated the sustained (1–72 h) effects of a hemodynamic stimulus on endothelial and vascular smooth muscle cell phenotype. The time course of many of these experiments makes translating this data challenging given that the beneficial effects of exercise on vascular health are derived from acute (30–60 min) bouts of physical activity and exercise that are performed daily over several months (19).

Another limitation that exists is that the profile and/or magnitude of the hemodynamic forces that were used in these chronic experiments did not simulate what occurs in vivo in conduit arteries supplying blood to the myocardium, skeletal muscle, and viscera during exercise. It is also important to note that the interactions between the multiple hemodynamic forces that change during exercise are rarely investigated, but likely play a significant role in the beneficial effects that exercise has on vascular health (13, 14). Adding another layer of complexity is the fact that regional differences in gene expression and atherosclerotic susceptibility occur both within and between arteries as a result of local hemodynamic stimuli (9, 77, 127). This heterogeneity of hemodynamic stimuli and gene expression throughout the vascular network makes generalizing in vitro data challenging.

Based on these limitations, it is important to acknowledge that utilizing data from in vitro preparations to determine the impact of exercise-induced hemodynamic forces on vascular health clearly oversimplifies a very complex signaling stimulus. For this reason it is imperative that data obtained from human in vivo paradigms be used in conjunction with knowledge derived from in vitro preparations to better understand how changes in hemodynamic forces during exercise may beneficially impact vascular health.

ROLE OF EXERCISE-INDUCED HEMODYNAMICS IN VIVO: HUMAN STUDIES

The strengths of an integrative human physiological approach to questions of vascular adaptation to exercise include direct applicability and clinical relevance (58). Upright posture, bipedal locomotion, competition for blood flow between competing vasculatures and the range of exercise interventions that can be adopted all make humans unique in terms of integrated cardiovascular responses to exercise and training. In the subsequent section of this review, we will consider the role of local and systemic hemodynamic factors in adaptations that occur in the human vasculature.

Acute exercise: shear stress and vascular function. Increases in flow or, more precisely, shear stress, transduce the release of vasodilator substances from the endothelium. For example, most studies that have infused competitive antagonists of NO production during postischemic increases in conduit artery shear stress have observed significant decreases in endothelium-dependent flow-mediated dilator (PMD) responses (21, 22, 56, 57, 60, 67, 80, 97). Such data reinforce key findings in animals (88, 93) and it is now generally accepted that shear stress is a principal physiological stimulus experienced by the endothelium in humans.

Studies of the impact of different forms of exercise-related shear on the endothelium in humans were prompted by the observation that lower limb exercise training induces upper limb vascular adaptation, suggesting a generalized or systemic impact of exercise on endothelial function (38, 68). Studies of the acute impact of different exercise modalities on upper limb blood flow therefore followed. During handgrip exercise, predominant increases in anterograde brachial artery flows occur during systole, in keeping with decreased distal vascular resistance associated with downstream vasodilation in the active skeletal muscle (30, 36) (Fig. 2). By comparison, cycle ergometer exercise was associated with lower mean blood flows through the brachial artery feeding the inactive upper limbs, but this concealed substantial changes in both systolic anterograde and diastolic retrograde flows (30, 36) (Fig. 2). It was subsequently established that different forms of lower limb exercise can induce different patterns of upper limb blood flow and shear stress (109). This work established that different patterns of blood flow and shear stress exist in humans during exercise, raising the possibility that vascular adaptations, including the production and bioavailability of NO (30, 35), may be differentially affected according to the nature of the hemodynamic and shear stress stimuli to which the endothelium are exposed.

Subsequent studies attempted to distinguish between the acute impact that different patterns of blood flow and shear stress on endothelial function in humans. In one series of
experiments, brachial artery endothelium-dependent flow-mediated dilation was assessed immediately before and after simultaneous bilateral exposure to forearm heating (submersion in 40°C water), handgrip exercise and lower limb cycle ergometry (114). Each of these stimuli involves different shear patterns, with predominant anterograde flows during the former interventions and oscillatory patterns during cycling. A pressure cuff was also inflated on one arm throughout each of the interventions to induce within-subjects differences in flow and shear patterns. The results of this experiment suggested that increases in anterograde flow and shear acutely enhance endothelial function, while there was also a suggestion that retrograde or oscillatory flows might diminish this favorable effect (Fig. 2). The latter possibility was later confirmed in an experiment in which a "dose-response" relationship was established between stepwise increases in retrograde shear and decreases in endothelial function (110).

Other factors can alter the effect of shear pattern on the endothelium. For example, it was found that the prominent retrograde shear during the first minutes of cycling training returns toward baseline levels when thermoregulatory cutaneous vasodilation occurs (101). These changes in shear stress in conduit arteries, but also in microvessels, may occur when exercising in the heat. Whether these changes in shear also lead to different vascular adaptations is currently unclear. It is also probable that the intensity and/or duration of exercise may alter the nature of acute changes in endothelial function. Data from Goto et al. suggested that low-intensity exercise may fall below a threshold for improvement in endothelial function, that moderate-intensity exercise enhances endothelial function and that, at higher intensities, endothelial function may not necessarily be enhanced, possibly due to competitive and detrimental impacts of elevated oxidative stress or inflammation (6, 28). Some recent studies provide limited support for this paradigm, as prolonged intensive exercise is associated with decreased endothelial function in humans (16); however, much work in this field remains to be done.

The studies described above indicate that vasodilation occurs in conduit arteries in humans in response to shear stress, that different patterns of shear stress occur in different vascular beds in response to exercise in humans, that different types or forms of exercise are associated with distinct hemodynamic and shear stress responses, that anterograde flow and shear are associated with acute enhancement in endothelial function, and that retrograde patterns may be acutely detrimental in this regard. From these findings we might postulate that shear-induced adaptations in vivo may depend upon the balance between anterograde and retrograde components of flow and also interactions with factors which impact upon endothelial function, such as inflammation and oxidative stress.
Exercise training: chronic episodic changes in shear stress and vascular function. Findings regarding the acute effects of exercise, described above, are pertinent to understanding the impact of repeated episodic exposure to exercise. In a study designed to isolate the impact that repetitive increases in shear stress have on endothelial adaptation, bilateral handgrip training was undertaken with a cuff placed around one arm to unilaterally decrease the shear stress associated with each exercise bout (113, 114). While training induced similar effects on forearm volume, girth, and strength in both limbs, vasodilator function improved only in the side exposed to increases in shear stress. These data suggest that shear stress is an important stimulus to vascular adaptation associated with exercise training in vivo. Nonetheless, exercise is a complex stimulus and it is possible that other impacts of training are responsible for some of the adaptations observed. A subsequent study therefore assessed the effect of repeated increases in shear stress, independent of exercise. This involved repeated episodic bilateral forearm heating, with a cuff inflated on one arm during each heating bout to “clamp” or decrease the increase in shear. Only the forearm not exposed to cuffing (and therefore elevated shear) demonstrated improvement in vasodilator responses, findings that were present at both conduit artery and microvessel levels (33, 83).

In summary the data described above, along with a large body of evidence pertaining to the impact of exercise training on endothelial function in humans reviewed elsewhere (39, 40, 111), reinforce the classic experiment of Hambrecht et al. (44), who cleverly demonstrated that in vitro and in vivo enhancement in endothelial function in the internal mammary artery in response to exercise training were associated with increased endothelium-derived NO synthase (eNOS) shear-related protein expression and phosphorylation.

Acute and chronic exercise: arterial pressure, shear stress, and vascular function. The importance of systemic pressure change during exercise, in terms of endothelial function, was suggested by a study in which heart rate (HR) responses were manipulated at rest in patients with implanted pacemakers to levels observed during incremental cycle exercise (34, 35). In the absence of increases in pulse pressure, increased HR was not associated with enhanced endothelial production of NO. While this study suggests that pressure change may be an important acute mediator of vascular function in vivo, it has been difficult to disentangle the impacts of changes in pressure per se from those in flow and shear stress. One recent study attempted to tease out this question by examining the acute impact of transmural pressure drop following cuff deflation on dilator responses (40, 56). The authors concluded that the true magnitude of the flow (shear) mediated dilator response after cuff deflation may be masked by opposing vasoconstriction caused by a drop in transmural distending pressure. These data indicate that acute interactions between the hemodynamic stimuli of pressure and shear may determine the ultimate vasoactive arterial response. The role of myogenic responses in this context remains to be determined (15, 40).

In terms of assessing the relative impact of pressure and shear on vascular adaptation in response to exercise training, one indirect approach is to compare changes observed in both limbs following a unilateral training stimulus. Small muscle group exercise, such as that involving hand-gripping, induces localized changes in shear stress without large impacts of central pulse pressure. Conversely, large muscle group repetitive dynamic exercise induces localized effects due to skeletal muscle vasodilation, along with systemic changes in blood pressure which impact on shear stress but also modulate transmural pressure. If training has localized (shear), but not systemic (pressure) effects, then adaptation should be isolated to the trained limb. In this context, elite tennis players possessed no evidence of difference in resistance vessel endothelial function in their preferred and nonpreferred limbs (37) and unilateral handgrip training also did not result in differential endothelial function in the preferred and nonpreferred arms (31). These findings suggest that endothelial function may not differ as a result of localized training in those exposed to chronic training stimuli, but it is important to note that several studies have observed impacts on endothelial function of localized (including handgrip) training regimes, especially in subjects with impaired endothelial function a priori (111).

Another systemic hemodynamic stimulus relates to circulating endothelial progenitor cells (EPCs), which represent immature cells that possess the capacity to contribute to the maintenance of endothelial integrity and function through differentiating into mature endothelial cells that replace damaged endothelial cells, but also initiate neovascularization (3). The importance of EPCs in humans is supported by the strong evidence provided from both animal and human studies. In vitro studies have shown that EPCs are induced by shear stress (45, 108), and that shear stress can stimulate EPCs to incorporate into the vasculature (38). In vivo studies have shown that EPCs are recruited into the arterial wall in response to injury (39, 40), and that EPCs can improve endothelial function (37), suggesting a role for EPCs in the maintenance and repair of endothelial function.

Fig. 3. Brachial artery (BA) diameter (A) and wall thickness (B) in the dominant (black bars) and nondominant arm (white bars) of elite squash players (n = 13) and matched controls (n = 16). Error bars represent SE. *Significantly different from the dominant side at P < 0.05. P value refers to a post hoc unpaired t-test between squash players and controls. Results from the 2-way ANOVA are presented in the figure. Data are adapted from Rowley et al. 2011 (92).
relation between EPCs and endothelial function (49). Studies in humans have found that acute exercise leads to EPC mobilization in healthy subjects (108, 120), but also in those with cardiovascular disease (1) or risk (108). Exercise training also increases levels of EPCs (63, 95, 104, 108). A study in eNOS-knockout mice and wild-type mice treated with NOS blockers showed an attenuated increase of EPCs in response to exercise training (63), which suggests an important role for the NO pathway for the release of EPCs during exercise. In addition to the effect of exercise on the quantity of EPCs, it is uniformly demonstrated that exercise training improves functional characteristics of EPC (52, 95, 107). Therefore, current evidence suggests that exercise training improves EPC function, which may contribute to exercise-induced vascular adaptations [see reviews (66, 107)].

**Acute and chronic exercise: arterial pressure, shear stress, and vascular structure.** One explanation for above disparity pertaining to the effects of localized training on endothelial function may relate to the time course of arterial adaptation and interplay between functional changes and adaptations in arterial size, or remodeling, which can occur in an endothelium-dependent manner (62, 116, 118). Laughlin originally suggested that structural enlargement of arteries may supersede functional adaptations that occur in the shorter term (64) and some recent human evidence supports this contention (113). Analysis of previous unilateral training data suggests that elite racquet sportsmen exhibit arterial enlargement at both resistance (37, 102) and conduit (54, 92) level and longitudinal handgrip training is also associated with artery remodeling (31, 103). Furthermore, Miyachi et al. (76) demonstrated that unilateral lower limb training induces changes in the size of the conduit artery in the exercised limb that were not apparent on the contralateral untrained side. These data suggest that shear stress-dependent mechanisms can induce localized endothelium-dependent changes in the size of arteries in vivo.

The question of whether exercise-mediated changes in arterial pressure can induce arterial adaptation is more difficult to answer in humans. Large pressure changes are more apparent in response to large muscle group exercise, but such exercise also impacts on blood flow and shear stress. Some studies have reported enhanced upper limb resistance artery vasodilator capacity following predominantly lower limb exercise training.
Acute changes in shear stress that modulate endothelial function is unclear at the moment. A recent proposal is that exercise-related arterial pressure may modulate arterial wall thickness (92). This idea owes much to the work of Folkow, who proposed decades ago that transmural pressure, wall thickness and wall-to-lumen ratio are related according to the law of Laplace (23, 24, 40). Whether the effects of exercise on wall thickness are local or generalized in nature is uncertain, with some studies suggesting that exercise modifies skeletal muscle wall thickness, but not that of the carotid artery (96), while others have observed training-induced changes in larger arteries (61, 74). In a recent study, the limbs of elite squash players were compared with matched healthy control subjects and lower wall thickness measures were apparent across carotid, brachial, and femoral arteries in the athletes (92). However, wall thickness did not differ between the preferred and nonpreferred limbs of the squash players despite increased arterial diameter specific to the preferred limb (Fig. 3). These data suggest that training may influence wall thickness via systemic, rather than localized mechanisms. However, it must be noted that the high fitness level of squash players may have masked local effects. While there are multiple nonhemodynamic systemic effects of exercise that may impact upon wall thickness (e.g., inflammation, oxidative stress), one explanation for these findings may be that the effect of exercise on arterial wall thickness may be pressure mediated, whereas shear-mediated impacts on arterial lumen size are more localized. However, research in this arena is in its infancy and much work needs to be done in humans to address questions of relative impacts of pressure and shear on arterial adaptation.

A final potential stimulus that may contribute to exercise-induced vascular adaptations relates to ischemia. Exercise can evoke repeated bouts of ischemia. Interestingly, repeated exposure of the vasculature to ischemia essentially reflects the phenomenon of ischemic preconditioning, which refers to the reduction of ischemia-reperfusion injury induced by a brief preceding period of ischemia (81). Whether exercise training leads to such cardioprotective effects via ischemic preconditioning is unclear at the moment.

**Acute and chronic exercise and vascular smooth muscle in humans.** Acute changes in shear stress that modulate endothelial function do not typically have an effect on the magnitude of the endothelium-independent vasodilation (114). Similarly, repeated episodic increases in shear stress associated with exercise (115) or heating (83) do not modulate smooth muscle sensitivity to NO, thereby likely isolating changes to the endothelial layer. These human data generally suggest that, with some exceptions (25, 69, 87), exercise training induces changes in endothelial, but not smooth muscle, vasodilator function (39, 111). Nonetheless, it must be borne in mind that assessment of vascular smooth muscle function in humans has classically been confined to administration of NO donors and measurement of peak vasodilator responses and it therefore remains possible that smooth muscle adaptation occurs but has not been detected due to the limitations associated with in vivo human research. The literature may therefore be biased by the limitations of these approaches. For example, animal data suggest that exercise training may alter gene expression and the phenotype of smooth muscle cells, potentially leading to a higher affinity to NO and/or more rapid responses. If similar changes also occur in humans, then the “kinetics” of response to smooth muscle vasodilators (e.g., onset time or rate of dilation) could provide important additional information regarding adaptation (112). In addition, almost all humans studies of smooth muscle conduit function use a single dose of vasodilator nitroglycerine, ignoring the possibility of dose-response changes (112).

As described above, it is clear that shear forces can induce changes in arterial lumen size in resistance and conduit arteries and this process is likely endothelium-mediated. Remodeling of tunica media must underlie this process, inferring an effect of shear stress on vascular smooth muscle growth and/or architecture. This is reinforced by studies which have reported that training can modify conduit artery wall thickness (20, 41, 71, 121), although the carotid artery may be an exception to this rule (79, 105) and resistance exercise (90, 96) may induce different responses to aerobic training.

Future studies should consider more complex approaches to the assessment of smooth muscle function in humans, particularly in light of the likely role of structural changes discussed above. The impact of exercise training on mechanisms other than NO-mediated smooth muscle dilation has not been studied in detail in humans.

**SUMMARY**

It is clear from both in vitro and in vivo experiments that hemodynamic stimuli play an important role in endothelial and vascular smooth muscle cell adaptations associated with physical activity and exercise training (Fig. 4). Current evidence suggests that the most potent of these hemodynamic stimuli is endothelial shear stress. However, the impacts that exercise-induced changes in hemodynamic profile, pulse pressure, transmural pressure and endothelial progenitor cells have on local and systemic vascular adaptations are still unclear. It is also unclear if the multiple hemodynamic changes that occur during exercise work individually or synergistically to produce changes in endothelial and vascular smooth muscle cell phenotype. Future research using complementary in vitro and in vivo models will be necessary to address these and many other questions highlighted in this review.

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