TO THE EDITOR: Animal investigations permit invasive techniques and a spatial and temporal resolution not feasible in humans. Thus structural and functional adaptations to exercise training within the muscle resistance vasculature (i.e., arterioles) can be observed directly and related to blood flow within the same muscle (3–5). This approach is powerful because the hemodynamic response differs substantially between the conduit artery and microvasculature (2).

When Lash and Bohlen (3) demonstrated increased diameter and enhanced functional vasodilation of 1A/2A arterioles in the spinotrapezius muscles of young rats trained for 8–10 wk (30 m/min, 2.5° incline, 80–90 min/day) the tacit presumption was that this muscle was recruited with the resultant hyperemic response during exercise training. However, the spinotrapezius muscle evidenced no increase in the sentinel oxidative enzyme citrate synthase in that investigation (3) nor does level or inclined running increase blood flow in this muscle (4).

Pursuant to the present debate (1, 6), these investigations (3–5) demonstrate structural/functional adaptations within arteriolar resistance vessels without a net hyperemic response. What remains to be resolved is the importance of key candidate mechanisms: endothelial stimulation via anteriograde and retrograde flow in the absence of net hyperemia (1), mechanical distortion of the vascular intima and endothelium, and a medley of humoral and neurally mediated effects.

In conclusion, animal studies provide evidence for both structural and functional microvascular adaptations to training in nonhyperemic (and therefore presumably nonrecruited) muscles (3, 5). Notwithstanding the above, without knowing the mechanistic basis or bases for such adaptations, broad extrapolation across multiple exercise training scenarios and species seems ill advised.

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TO THE EDITOR: Before turning the debate (1, 6) into a battle we should make sure to ask the correct question. Is the question really if physical training induces vascular adaptations beyond active muscle beds?

Let us therefore start with the very basic issues: Which factors are important to increase endothelium-dependent vascular dilatation (EDD) in a given vascular bed? We would agree that any physical activity leading to an improvement in regional EDD should 1) either involve the limb that is studied to increase local blood flow, or 2) cause an increase in cardiac output large enough to accelerate local blood flow and to activate shear-stress related signaling at the level of endothelial cells, or 3) should generate an increase in VEGF and NO large enough to effect endothelial progenitor cells (3, 5) to mediate systemic effects on EDD (4). Points 2 and 3 clearly depend on a threshold of 1) muscle mass involved, 2) exercise intensity, 3) exercise duration, and 4) type of exercise (resistance vs. endurance). What we need is therefore not a debate of general beliefs but a detailed investigation of the different studies that fulfill the conditions outlined above. Additionally, we need innovative study designs that systematically assess the mechanisms that are important for systemic vascular effects (increase in cardiac output, blood pressure amplitude, regional blood flow) and the increase in important vascular mediators (NO, VEGF, EPCs). Since these parameters were not measured in the majority of studies we are in a position where simplistic concepts may lead to inappropriate controversies.

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TO THE EDITOR: The question whether exercise induces adaptations in nonactive muscle arteries (1, 5) cannot be answered by a simple yes or no. We believe that the effect in nonactive muscle beds is best viewed as a balance with the individual’s...
exercise tolerance, lipid and glucose status, and blood pressure on the one side, and exercise intensity and degree of improvement of lipid, glucose, and blood pressure status on the other side. A low-intensity exercise program in healthy subjects, by abovementioned measures, may therefore induce little or no improvement in endothelial function, whereas a high-intensity program might (3). In contrast, in situations of reduced cardiovascular and metabolic health, such as heart failure, hypertension, diabetes, and hypercholesterolemia, exercise may readily improve endothelial function in all vascular beds. This has been suggested by both brachial artery plethysmography and imaging, and organ bath experiments of the left internal mammary artery (2, 6). Further support for exercise-induced adaptation in nonactive arteries stems from studies of treadmill-exercised rodents, which improve carotid artery endothelium-dependent nitric oxide (NO)-mediated vasorelaxation (4). Supposedly, the carotid artery does not supply exercising muscles. Intracellularly, improved endothelial function has been linked to high activities of endothelial NO synthase and Akt (2), suggesting the cell may sense shear stress even in nonactive regions. Thus clinical and experimental evidence suggest that the artery is in a state of continuum, in which the susceptibility for changes depends more on the state of the artery and on exercise intensity, rather than the location.

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TO THE EDITOR: Green and colleagues conclude with the assertion that a “generalized functional vascular adaptation induced by exercise training is a known known” (2). It is unclear what Green et al. mean by “generalized” but it seems to mean systemic adaptations in most, if not all, inactive vascular beds (even outside the arm and leg vasculatures).

Animal studies demonstrate training-induced functional adaptations, characterized by enhanced endothelium-dependent dilation (EDD), in inactive vasculatures, thus lending some support to this conclusion. For instance, the rabbit renal vasculature and rat carotid artery demonstrate enhanced EDD following training; however, other inactive vasculatures do not (1, 3). In addition, enhanced EDD of rat spinotrapezius arteries, which does not have increased blood flow during exercise, has been demonstrated (5). This supports the argument that large increases in blood flow are not necessary for training-induced adaptations, even in muscle tissue.

Green et al.’s contention that an enhanced oscillatory shear profile in inactive vascular beds may account for these adaptations remains to be tested. In fact, in vivo and in vitro data strongly suggest that oscillatory shear produces a proatherogenic endothelial phenotype (4). Thus it seems likely that other factors, perhaps circulating or autocrine/paracrine, as suggested by Thijssen and colleagues (6) are involved.

We surmise that available evidence from animal models suggests that functional vascular adaptations, encompassing muscular and visceral tissues, are induced by exercise training outside of active beds through a still fully unknown mechanism. It is not supported, however, that training produces these adaptations in all inactive vascular beds.

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TO THE EDITOR: We read the Point:Counterpoint regarding blood flow to the nonworking limb with great interest (3, 6). Previous studies have already indicated that the blood flow in nonexercising limb increased and the increase was exercise intensity dependent (2, 4, 5). Recently, we found that the change in blood flow in nonexercising limb was not only exercise intensity dependent but also time dependent (7). We determined the effect of exercise intensity, time of one-legged exercise, and the interaction between these two variables on the blood flow in the contralateral nonexercising leg during dynamic knee extension exercises. Biphase time-dependent changes were observed: an initial increase (vasodilation) at the onset of exercise and a subsequent decrease (vasoconstriction) as exercise proceeded, probably due to an augmented muscle sympathetic nerve activity. In this study, EMG recording during exercise confirmed that the nonexercise limb was certainly “inactive.” In addition, the difference of limbs used for exer-
Exercise and blood flow study should be considered because forearm and leg vasculatures are differentially controlled during exercise, and different types of exercises present different hemodynamic stimuli to the endothelium, which may result in differential effects of shear stress on the vasculature. The mechanism underlying exercise training-induced vascular adaptation in nonexercising limb is consistent with our idea: 12 wk of moderate-intensity exercise, but not mild-intensity or high-intensity exercise, had beneficial effects on endothelial function (1). Thus the discrepancy between Green et al. (3) and Thijssen et al. (6) may be attributed in part to differences in exercise intensity, its time, and/or limb studied. Accordingly we can support ideas of both Green et al. and Thijssen et al.

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