Point:Counterpoint: Exercise training does/do not induce vascular adaptations beyond the active muscle beds

POINT: EXERCISE TRAINING DOES INDUCE VASCULAR ADAPTATIONS BEYOND THE ACTIVE MUSCLE BEDS

A few years ago we published a series of studies that investigated the impact of exercise training on vascular function in humans (20–22, 26–29). All of these studies involved a similar exercise training intervention, a combination of resistance and aerobic exercise, performed under close supervision, which we referred to as circuit training (CT). In some of these studies we examined upper limb conduit artery function (20, 26–29), but our main interest was in resistance vessel adaptations, assessed using intrabrachial infusions of acetylcholine, sodium nitroprusside, and sometimes monomethyl-L-arginine, with measurement of forearm blood flow responses. In all of our circuit training studies, subjects avoided hand grip exercise: while cycling or on the treadmill, subjects were asked not to grip the handle bars or railings and this was policed by the supervising exercise physiologist (usually AJM). We also avoided all upper limb resistance exercises that involved gripping the equipment. Nonetheless, for largely historical reasons (most previous studies had used the forearm as a model), we studied vascular adaptations in the upper limb before and after this lower limb training. Our studies therefore indicated that predominantly lower limb exercise was associated with vascular adaptations in the upper limbs, where direct exercise had in fact been avoided. Around this time a paper from Rainer Hambrecht’s group (19), entitled “...: Systemic [vascular] effects of lower limb exercise” was also published and a review of the previous literature (12) suggested some improvements in upper limb vascular function as a result of predominantly lower limb exercise (4, 5, 13, 17), although many of these studies did not report whether subjects were requested to avoid incidental hand gripping. In any case, the possibility that there may be a generalized effect of exercise in vascular beds other than those where the exercise stimulus was focused, piqued our interest.

It was, of course, well established at this time that the principal physiological stimulus to improvement in endothelial function, and indeed arteriogenic structural adaptation, was shear stress on the endothelium, which transduced some of its effects through changes in nitric oxide (NO)-mediated vasodilator and mitogenic function (3, 12). If leg exercise training was leading to adaptations in the untrained upper limbs, perhaps this related to shear stress changes in the upper limb during lower limb activities? We therefore undertook studies to simply describe the pattern of blood velocity and flow through the resting upper limbs during cycle exercise. The traditional wisdom at the time was that, being an inactive vessel bed during lower limb exercise such as cycling (the arms were passively supported in these experiments), blood flow in the upper limbs should not increase greatly and, as a proportion of cardiac output, it may even decrease so that O2 transport is focused on the active lower limbs. Historical studies that had established this redistribution concept relied on plethysmography or measurement of limb a-VO2Δ (1, 2, 14), techniques that only provide a global index of total or average flow into the limb. In our experiments we used high-resolution Doppler ultrasound for which we had developed edge detection and wall tracking algorithms that allowed us to calculate blood flow change across the cardiac cycle at ~30 Hz (11).

When subjects started upright cycling, we observed an interesting change in the pattern of blood flow in the brachial artery of the inactive upper limbs. Although the mean flows changed in a manner that was broadly consistent with the plethysmographic prediction (2), this data camouflaged a large underlying change in the pattern of flow. Along with increases in anterograde flow during systole as cardiac output increased, we observed large increases in the magnitude of retrograde flow during diastole when subjects began cycling (11). The “amplitude” of flow increased with exercise intensity. Significant volumes of blood therefore flow backward toward the heart during diastole, a finding that might have surprised William Harvey!

The shear stress-sensitive endothelium therefore does not see a smooth increase in laminar anterograde flows in the upper limbs as cycle ergometer intensity increases, but rather, somewhat large oscillations in flow whereby blood is dragged in both directions across the cell membranes. Simplistically, we assumed that this might represent a greater stimulus to endothelial NO production or bioavailability than a simple increase in largely anterograde laminar flows. The next step then was to determine whether this pattern of flow in the brachial artery of the resting upper limb induced NO release during cycling (10). We found that the effect of NO blockade during incremental cycling exceeded, albeit slightly, that observed during incremental hand grip exercise, despite both types of exercise resulting in similar average blood flows into the limb (8). It seems, therefore, that the mode and intensity of exercise performed has important implications for the pattern of flow, notwithstanding the presence of similar bulk flows over time. If endothelial phenotype is indeed sensitive to flow and shear stress patterns (18), then different types of exercise may logically result in different endothelial adaptations and, consequently, different degrees of change in the health of the vessel wall and its predisposition to atherogenic change (7, 9, 30). Interestingly, studies of endothelial cells in culture suggest that some oscillatory flow patterns produce proatherogenic gene expression, decreased NO bioavailability, and promote endothelial dysfunction (18). As Oscar Wilde put it, “Consistency is the last refuge of the unimaginative.”

The exercise training studies described above suggest that functional vascular adaptation might be a generalized consequence of large muscle group activity, a suggestion also supported by studies of carotid artery compliance following leg exercise training (25). Can arterial structural change occur in regions that are not directly involved in the training stimulus? Some studies that have examined resistance vessel structure indicate that leg exercise increases peak forearm blood flow (24), whereas studies of conduit arteries have not typically exhibited adaptation in nonexercised regions (6, 16). The jury is therefore still out on globalized structural adaptation, although it is well established that the size of large arteries
feeding active muscle beds, including coronary arteries, increases with training (3, 12).

So, in all, we suggest that there is substantial extant evidence that predominantly lower limb exercise generates changes in upper limb vascular function (e.g., Refs. 4, 5, 7, 15, 17, 19–21, 23, 26, 27, 30)—there are many others). The explanation for these findings remains unclear, but one possibility relates to the impact of shear stress throughout the vasculature, since the hemodynamic impact of exercise is not specific to the locally trained region when the mass of muscle engaged in the exercise is large. Other explanations can be speculated, including the release of vasodilator agents from active muscle beds and their subsequent circulation to inactive regions. But we are not currently aware of any evidence for this in humans. At the very least, we believe there is sufficient evidence that exercise training does induce vascular adaptations beyond the active muscle beds that we might begin to suspend our collective scientific disbelief.

The proposition that exercise training induces generalized functional vascular adaptations seems to us, on the basis of the evidence, a known known. Whether training induces systemic structural vascular adaptation remains a known unknown. As always, we look forward to the future challenge of the many unknown unknowns (not Oscar Wilde).

GRANTS

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REFERENCES


Exercise training is a well known and powerful strategy to improve cardiovascular structure and function in healthy individuals as well as in patients with various diseases (10). It has been suggested that exercise-induced vascular adaptations, at least partly, explain the decrease in cardiovascular risk (11). Therefore, insight into localization and magnitude of exercise-induced vascular adaptations is essential to optimally benefit from exercise training to improve vascular health. Previous studies that examined the effects of exercise training in animal studies primarily evaluated the exercised hindlimbs (5, 29), whereas molecular responses to cycling exercise in humans were analyzed from biopsies taken from the highly active quadriceps muscle (7, 12). In contrast, studies examining vascular adaptations to lower limb training (e.g., cycling, walking, and running) mainly focus on the nonactive forearm vascular bed. This is even more surprising considering the stimuli for arteriogenesis and angiogenesis during exercise training, i.e., increments in blood flow and shear stress on the endothelium and reduced oxygen tension and related expression of vascular endothelial growth factor. During cycle exercise, blood flow and oxygen consumption only minimally increase in the nonactive upper limbs (1, 9, 24). Accordingly, vascular adaptations are unlikely to be expected in inactive regions.

While many previous studies examined lower limb exercise-induced vascular adaptations in one region (e.g., forearm; Refs. 4, 14, 17, 23, 30), only a few studies assessed adaptations in the active leg as well as in the nonactive upper extremity. Interestingly, these latter studies reported vascular adaptations in the exercised region, but not in the nontrained vascular beds. For example, in 40 patients with coronary artery disease, 10-wk (predominantly cycling and walking) exercise training resulted in an improved posterior tibial artery endothelial function and reduced oxygen tension and related expression of vascular endothelial growth factor. During cycle exercise, blood flow and oxygen consumption only minimally increase in the nonactive upper limbs (1, 9, 24). Accordingly, vascular adaptations are unlikely to be expected in inactive regions.

Despite the above findings, several studies, which examined the forearm only, reported functional and structural vascular adaptations to lower limb exercise training (e.g., walking, running, and cycling) in the nonactive brachial (30) and radial artery (17) or forearm vasculature (4, 14, 23). Especially during walking and running exercise, which involves upper body movements, the nonactive forearm vascular bed is at least moderately active. Apparently, the angiogenic stimuli shear stress and hypoxia exceeded the threshold to induce vascular adaptations in the nonactive forearm vascular bed in these studies (4, 14, 17, 23, 30). On the basis of this limitation in many in vivo studies, vascular adaptations in nonactive regions do not necessarily result from the exercise training stimulus in the lower limbs per se.

Accurately addressing the question whether exercise training induces vascular changes in nonactive areas is challenging, especially when examining large muscle mass exercise. Studying individuals with a spinal cord injury (SCI) offers a unique opportunity to examine active and nonactive areas during exercise training. Below the lesion level, SCI individuals are subject to a complete loss of motor and sensory control, excluding the possibility for “polluting” muscle activity in the paralyzed muscles during exercise. Accordingly, arm-crank exercise in SCI individuals offers the opportunity to study whether leg vascular function adapts in the paralyzed legs. Although involving a smaller muscle mass than cycling, arm-crank exercise can result in ~80% of maximal oxygen uptake and ~90% of maximal heart rate (18, 22). A previous cross-sectional study examined the effects of upper extremity exercise training on artery size above and below the lesion level in paraplegic endurance athletes (n = 29) and inactive paraplegic subjects (n = 20). The ~50% higher physical fitness level and doubling in cross-sectional area of the subclavian artery in the paraplegic endurance athletes compared with sedentary paraplegics indicates the difference in upper extremity activity level between both paraplegic groups. Nonetheless, both groups demonstrated similar femoral artery dimensions (13), which reinforces our hypothesis.

Functional electrical stimulation (FES) in SCI individuals provides the opportunity to stimulate individual paralyzed muscle groups. FES cycling substantially increases heart rate and oxygen uptake (20) and is demonstrated to change leg vascular function after at least 2 wk training (27, 28). Adjacent, nonstimulated paralyzed regions are subject to passive movement, while no polluting muscle activity will be present. Since passive movement does not induce acute or chronic blood flow changes (25), these regions provide a unique opportunity to study the effects of exercise training in active and adjacent, nonactive muscles. Recently, we studied vascular adaptations before and after 4 wk of FES cycling in the stimulated thigh muscles and the adjacent inactive calf in SCI individuals (28). While functional and structural vascular adaptations were reported in the thigh, no exercise-induced vascular changes were reported in the calf vascular bed. In another study, 4-wk unilateral limb stimulation in SCI individuals significantly changed superficial femoral artery structure and function of the trained leg, whereas vascular characteristics in the untrained leg were not altered (2). These findings demonstrate the pres-