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

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Point: “Exercise training does induce vascular adaptations beyond the active muscle beds.”

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A few years ago we published a series of studies which 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, assayed using intrabrachial infusions of acetylcholine, sodium nitroprusside and sometimes LNMMA, with measurement of forearm blood flow responses. In all of our circuit training studies, subjects avoided hand grip exercise: whilst 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 generalised effect of exercise in vascular beds other than those where the exercise stimulus was focussed, 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 focussed on the active lower limbs. Historical studies which had established this redistribution concept relied upon 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 utilised 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 around 30Hz (11).

When subjects started upright cycling, we observed an interesting change in the pattern of blood flow in brachial artery of the inactive upper limbs. Although the mean flows changed in a manner which 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 backwards towards the heart during diastole, a finding which 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 pro-atherogenic 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 generalised 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 which 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 non-exercised regions (6, 16). The jury is therefore still out on globalised 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. (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 generalised 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).

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References


**Counterpoint:** Exercise training **does not** induce vascular adaptations beyond the active muscle beds

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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 hind limbs (5, 29), while 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 non-active 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 upon 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 non-active 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 1 region (e.g. forearm) (4, 14, 17, 23, 30), only a few studies assessed adaptations in the active leg as well as in the non-active upper extremity. Interestingly, these latter studies reported vascular adaptations in the exercised region, but not in the non-trained vascular beds. For example, in 40 patients with coronary artery disease, 10-week (predominantly cycling and walking) exercise training resulted in an improved posterior tibial artery endothelial function, with no change in brachial vascular function (8). In addition, adaptations in lower limb conduit and resistance artery function and structure were found after 4-6 weeks electrically stimulated cycle-training in spinal cord-injured individuals (27, 28), 3 months cycling training in heart failure patients (3, 15), 12 weeks walking exercise in heart transplant recipients (21) and 3 weeks (19) to 1 year (6) lower limb
training in post-myocardial infarct patients, while forearm vascular function and structure did not change. This indicates that large-muscle mass exercise in these studies induced insufficient stimuli in the non-active forearm to result in vascular adaptations.

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 non-active brachial (30) and radial artery (17) or forearm vasculature (4, 14, 23). Especially during walking and running exercise, which involves upper body movements, the “non-active” 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 “non-active” forearm vascular bed in these studies (4, 14, 17, 23, 30). Based on this limitation in many in vivo studies, vascular adaptations in “non-active” 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 non-active 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 non-active 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 weeks training (27, 28). Adjacent, non-stimulated 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, non-active muscles. Recently, we studied vascular adaptations before and after 4 weeks 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 week 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 presence of local exercise-induced vascular adaptations, while contra-
lateral or adjacent regions from the exercised area do not benefit from the exercise training.

Taken together, we conclude that exercise does not induce vascular adaptations beyond
the active muscles. Most likely, if vascular adaptations in the “non-active” regions were
present, these regions were moderately active during exercise training, resulting in
changes in shear stress acting upon the endothelium and small increases in oxygen
consumption and hypoxia. Although these changes in shear stress and oxygen
consumption in the non-active regions are likely to be much lower than in the exercised
region, both stimuli may exceed the minimum level necessary to result in vascular
adaptations. Accordingly, active regions may demonstrate functional and structural
vascular changes at an earlier stage than the non-active muscles, leading to a possible
underestimation of the effects of exercise training when examining the non-active
muscles only. Therefore, future studies that examine the effects of physical (in)activity on
the vasculature should examine active as well as non-active regions. Many human in vivo
studies automatically choose to examine forearm vascular adaptations to assess the
effects of exercise training. However, calf and thigh baseline and peak blood flow using
plethysmography reported a good reproducibility (26), while the superficial femoral
artery FMD response represents a largely NO-mediated endothelium-dependent
vasodilation (16). This indicates the robustness of these tools to examine lower limb
vascular function and structure of conduit and resistance vessels in humans in vivo.
References:


Rebuttal

“Exercise training does induce vascular adaptations beyond the active muscle beds.”

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We sincerely thank our friends from Nijmegen for a stimulating debate.

We respond:

1. They quote “a number papers that have failed to demonstrate upper limb vascular adaptation to lower limb training”. Twenty-two of the 30 papers that have studied upper limb function after lower limb exercise have demonstrated adaptations (Table). Some of those quoted as contrary actually showed similar upper and lower limb changes (2) and, as our antagonists suggest, others may not have achieved a systemic hemodynamic/shear stimulus sufficient to induce global adaptation (8).

2. After acknowledging shear stress as a stimulus to vascular adaptation, they state that BF only minimally increases in the non-active upper limbs during leg exercise. Even if mean flows do not substantially increase, large changes in the pattern of flow can occur (3, 7). The flow/shear pattern presents to the artery wall as a stimulus.

3. They propose that leg exercise involves “moderate” arm activity which explains the vascular adaptation. We cannot speak for other studies, but we demonstrated forearm arterial adaptation despite upper limb exercise
being largely avoided (5, 6, 9, 10). Also, cycling causes substantial upper limb shear pattern changes, that induce NO release, when the forearms are passively supported (3, 7).

4. FES (Functional Electric Stimulation) in SCI (spinal cord injury) is proposed as a model in which the CFA (common femoral artery) experiences a shear stress/hemodynamic stimulus sufficient to induce vascular adaptation, yet the SFA (superficial femoral artery), 5cm downstream, does not (8). In this paper (pg 1116), an explanation is given that “Apparently, the stimulus [shear] is not sufficient to induce vascular adaptation [in the SFA]...” This is an implicit acknowledgment of our argument, ie where large muscle group exercise does cause a shear/pressure stimulus of sufficient magnitude, such a stimulus can induce vascular adaptations in itself, without localized muscle activity. In another study of SCI subjects, who represent a model of upper limb exercise training, preserved/enhanced FMD was observed in the SFA (1)!

Consensus?

“Arguments are to be avoided: they are always vulgar and often convincing” (Wilde)

We agree that there is little extant evidence that training induces structural adaptations beyond the active muscle beds. We also agree
that the nature of the exercise stimulus might determine whether shear/pressure signals are sufficient to induce functional adaptation in non-active beds. Different types of exercise certainly induce different shear/hemodynamic patterns (3). We propose the adoption of direct vascular flow/shear measurements during exercise to quantify the stimulus to vascular adaptations (4).

References


Table. Studies of the impact of lower limb exercise training on upper limb vascular function in humans

<table>
<thead>
<tr>
<th>Health status</th>
<th>Studies</th>
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<tbody>
<tr>
<td><strong>Healthy subjects:</strong></td>
<td>Kingwell et al. <em>Am J Physiol</em> 1997 ↑</td>
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<td></td>
<td>Higashi et al. <em>Circulation</em> 1999 ↑</td>
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<td>DeSouza et al. <em>Circulation</em> 2000 ↑</td>
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<td></td>
<td>Goto et al. <em>Circulation</em> 2003 ↑, ↔</td>
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<td></td>
<td>Pullin et al. <em>J Ex Physiol</em> 2004 ↑</td>
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<td></td>
<td>Moriguchi et al. <em>Hyper Res</em> 2005 ↔</td>
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<tr>
<td></td>
<td>Bergholm et al. <em>Atherosclerosis</em> 1999 ↓</td>
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<tr>
<td><strong>Hypercholesterolaemia:</strong></td>
<td>Lewis et al. <em>Arterio Thomb Vasc Biol</em> 1999 ↑</td>
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<td></td>
<td>Walsh et al. <em>Eur H J</em> 2003 ↑</td>
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<tr>
<td><strong>Hypertension:</strong></td>
<td>Higashi et al. <em>Circulation</em> 1999 ↑</td>
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<td></td>
<td>Moriguchi et al. <em>Hyper Res</em> 2005 ↑</td>
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<td></td>
<td>Linke et al. <em>J Am Coll Cardiol</em> 2001 ↑</td>
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<td></td>
<td>Belardinelli et al. <em>EJCVPR</em> 2006 ↑</td>
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<td>Dziekan et al. <em>Am Heart J</em> 1998 ↔</td>
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<td></td>
<td>Kobayashi et al. <em>Circ J</em> 2003 ↔</td>
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<tr>
<td><strong>Diabetes:</strong></td>
<td>Maiorana et al. <em>J Am Col Cardiol</em> 2001 ↑</td>
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<td>Fuchsjager-Mayrl et al. <em>Diabetes Care</em> 2002 ↑</td>
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<td>Xiang et al. <em>Diabetes Care</em> 2004 ↑</td>
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<td><strong>CAD:</strong></td>
<td>Walsh et al. <em>J Appl Physiol</em> 2003 ↑</td>
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<td></td>
<td>Edwards et al. <em>Am J Cardiol</em> 2004 ↑</td>
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<td></td>
<td>Gocke et al. <em>Am J Cardiol</em> 2002 ↔</td>
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<tr>
<td><strong>Peripheral artery disease:</strong></td>
<td>Andreozzi et al. <em>Int Angiol</em> 2007 ↑</td>
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↑ indicates enhanced upper limb vascular function following predominantly lower limb exercise training intervention. ↔ indicates no change. ↓ indicates reduced function. * Goto found enhanced function with moderate intensity training, but no change with low or high intensity training.
Rebuttal

“Exercise training does not induce vascular adaptations beyond the active muscle beds.”

Reading through Drs. Green, Maiorana and Cable’s argumentation, we hit on another Oscar Wilde’s wisdom: “the truth is rarely pure and never simple”.

In a series of experiments, Dr Green and colleagues demonstrated that typical changes in shear pattern, characterized by an increase in retrograde flow, are linked with endothelial NO release in the non-active regions (4). Although it might be tempting to relate vascular adaptation in inactive regions to alterations in shear pattern, we believe that the truth is not that simple. In non-active vascular beds during exercise, an enhanced release of vasoconstrictors is present, such as endothelin-1 (5), angiotensin II (7) and vasopressin (8). The actions of these local vasoconstrictors, combined with enhanced activity of the sympathetic nervous system (2), likely outweigh the beneficial effects of NO.

The role for shear rate in exercise-induced vascular adaptations is well recognized, but shear rate is not the only factor involved; unfortunately the truth is never simple. Hypoxia, through release of growth factors such as VEGF, importantly contributes to exercise-induced vascular adaptations (6). Notably, hypoxia and VEGF also contribute to the release and homing of circulating bone-marrow derived endothelial progenitor cells
(1). These progenitor cells predict the occurrence of cardiovascular events and death (9), possibly through their capability for endothelial repair, arteriogenesis and angiogenesis. Appreciating a key role for hypoxia in exercise-induced vascular adaptations, casts doubt on vascular adaptations in non-active muscles during exercise where this essential physiological stimulus is absent (3).

Interestingly, blood flow and related shear patterns vary markedly among different locations and sizes of arteries at rest and during exercise. The prominent retrograde component in the non-active brachial artery blood flow pattern is hypothesized to result from an increased downstream vasoconstriction (4). In contrast, arteries supplying highly metabolic tissues (i.e. heart and legs) have marked vasodilation and will therefore not demonstrate this blood flow pattern. Therefore, one may question whether findings in the brachial artery during leg exercise can be extrapolated to the coronary vascular bed, since shear rate as well as other physiological stimuli will be markedly different.

Taken together, the central question in this discussion is which stimuli are obligatory, either alone or in combination with others, to result in exercise-induced vascular adaptations in the active and non-active regions. We enjoyed discussing this topic and hope we presented our arguments in line with Oscar Wilde’s “one should always play fairly when one has the winning cards”.

Dick Thijssen
Maria Hopman
References:


