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Exercise and Vascular Function – How Much is too Much?

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Abstract

Exercise is a powerful therapy for preventing the onset and slowing the progression of cardiovascular disease. Increased shear stress during exercise improves vascular homeostasis by both decreasing reactive oxygen species and increasing nitric oxide bioavailability in the endothelium. While these observations are well accepted as they apply to individuals at risk for cardiovascular disease, less is known about how exercise, especially intense exercise, affects vascular function in healthy individuals. This review highlights examples of how vascular function can paradoxically be impaired in otherwise healthy individuals by extreme levels of exercise, with a focus on the causative role that reactive oxygen species play in this impairment.

Keywords

Exercise; Reactive Oxygen Species; Vasodilation; Nitric Oxide; Flow Mediated Dilation

Introduction

A delicate balance between reactive oxygen species (ROS) and nitric oxide (NO) exists within the vasculature. If the regional, subcellular concentrations of ROS increase beyond homeostatic levels in endothelial cells, vascular NO signaling can become corrupted, resulting in endothelial dysfunction which is manifested by vascular inflammation and proliferation (Forstermann 2010). Over time, this can lead to atherosclerosis and ultimately to cardiovascular events and increased mortality. A cornucopia of approaches has been proposed to mitigate the onset of endothelial dysfunction; however, routine physical exercise is universally considered one of the most powerful preventive and therapeutic interventions for cardiovascular disease (Naci and Ioannidis 2013). The beneficial effects of regular exercise are multifaceted, and prominently include an improvement in vascular function, which in part derives from a reduction in cellular ROS and restoration of NO bioavailability (Figure 1). While the shift in the ROS/NO balance to favor NO improves vascular function and cardiovascular outcomes, recent evidence suggests that a “tipping point” may exist, whereby too much exercise becomes detrimental to the cardiovascular system (Nikolaidis et al. 2012). As with many physiological stimuli or lifestyle choices, a threshold may exist beyond which there are diminishing returns, or frankly, adverse effects. Indeed a U-shaped curve has been suggested with regard to exercise, where either extreme

levels of activity or pronounced sedentary activity can be unhealthy, disrupting the NO/ROS balance similar to what is seen in cardiovascular disease. While this “exercise hormesis” theory has been described previously (Ji et al. 2010; La Gerche and Prior 2007; Radak et al. 2005; Radak et al. 2008) (Figure 2), the unique focus of this review will be on vascular-specific adaptations to extreme resistance and endurance training, highlighting the detrimental role of increased ROS in the maladaptive processes observed at the extremes (both high and low) of exercise behavior.

The Sedentary Lifestyle and Cardiovascular Health

Individuals who engage in regular exercise and physical activity have significantly lower rates of disability and an average life expectancy approximately seven years longer than their sedentary counterparts (Chakravarty et al. 2008; Sarna et al. 1993). While no exact definition exists for what constitutes a “sedentary lifestyle”, it is generally agreed that activities which have a metabolic expenditure of <2.0 metabolic expenditure of task (MET) units, such as sitting, reading, watching television or driving a car, are considered sedentary. The first study to directly link a sedentary lifestyle with increased cardiovascular mortality was published by Morris *et al* in 1953. In this study, bus drivers who spent their workday seated had double the incidence of fatal coronary artery disease (CAD) compared to moderately active individuals (Morris et al. 1953). Over the subsequent six decades several large cohort studies essentially confirmed these findings, establishing that a sedentary lifestyle positively correlates with an increased incidence of cardiovascular disease and death (Ford and Caspersen 2012).

How much inactivity is required to affect vascular structure and function? The most commonly used model to study the effects of inactivity on vascular function is the prolonged bed rest model. In a study involving 16 healthy male volunteers, after 25 days of bed rest a 13% reduction in femoral artery diameter was observed. Interestingly, this remodeling could be prevented by resistive vibration exercise (Bleeker et al. 2005). Indirect evidence also exists for microvascular remodeling with extreme inactivity. Bedridden healthy volunteers have a 22% reduction in the reactive hyperemic response after 5 days, and a 38% reduction after 52 days (Bleeker et al. 2005; Hamburg et al. 2007; Shoemaker et al. 1998).

The impairment of microvascular reactivity after bed rest also includes endothelial dysfunction. Hesse et al. demonstrated impaired acetylcholine-mediated increases in forearm blood flow after 13 days of bed rest (Hesse et al. 2005), while others have shown that as little as 7 days of bed rest can reduce basal blood flow and endothelium-dependent and – independent vasodilation in the skin microcirculation (Navasolava et al. 2010). While these models of sudden and profound inactivity uniformly show a reduction in vasodilator capacity and structural remodeling, they must be interpreted with caution as their extreme nature may not accurately represent a “real life” sedentary human lifestyle.

It is not known how much inactivity is required to induce vascular dysfunction. However the relationship between time spent performing sedentary activities and markers of inflammation and increased ROS has been examined. A large population-based study conducted in Iran showed that C-reactive protein (CRP), a marker of inflammation

commonly associated with coronary heart disease, was significantly elevated in the least active tertile of over 3000 adults (Esteghamati et al. 2012). The relationship between inactivity and markers of inflammation was further examined in a study conducted by Henson et al in participants at risk for type II diabetes. In that population, a strong correlation between sedentary time (as measured with an accelerometer) and plasma levels of CRP and interleukin-6 was observed (Henson et al. 2013), suggesting that the level of cardiovascular risk factors increases proportionately with longer durations of sedentary activity.

Vascular Adaptations to Exercise

It is of the general opinion of experts that physically active individuals may have approximately half the incidence of CAD as their most sedentary counterparts (Thompson et al. 2003) – rates that exceed those reported in large multicenter trials for antihypertensive and lipid lowering medications (Turnbull 2003; Wilt et al. 2004). Large survey-based studies have also shown a strong, dose-dependent, inverse relationship between physical activity and coronary heart disease (Tanasescu et al. 2002). As a therapeutic intervention, exercise training has been unequivocally shown to improve endothelial function in individuals with coronary artery disease (Edwards et al. 2004; Gokce et al. 2002), hypertension (Higashi et al. 1999; Moriguchi et al. 2005), hypercholesterolemia (Lewis et al. 1999; Walsh et al. 2003), obesity (Sciacqua et al. 2003; Watts et al. 2004a; Watts et al. 2004b), diabetes (Lavrencic et al. 2000; Maiorana et al. 2001a), and in the elderly (Black et al. 2008). In many instances, these individuals who show improvements in vascular function also have a concurrent reduction in overall mortality.

The term “athlete’s artery” was recently introduced by Green *et al* to describe the beneficial structural and functional adaptations that occur in the vasculature in response to exercise (Green et al. 2012). While a full discussion of these exercise-induced changes is beyond the scope of this review, key changes observed in trained athletes include increased muscle capillary density, larger conduit arterial cross sectional area, and increased nitric oxide bioavailability. However, studies designed to look at effects of exercise training on endothelium-dependent vasodilation in healthy individuals have yielded conflicting results, ranging from slight improvement (DeSouza et al. 2000; Higashi et al. 1999; Kingwell et al. 1997), to no change (Maiorana et al. 2001b), or in cases of extreme exercise, frank reductions in endothelial function (see below) (Bergholm et al. 1999; Goto et al. 2003). This wide variability has been explained in two ways, 1) vascular function may not be augmentable past a “normal” state of health, and 2) that over-training can actually reduce vascular health, consistent with exercise-related vascular hormesis model.

Exercise Intensity and Vascular Health

Determining the intensity and specific type of exercise that yields optimal cardiovascular benefit is an area of ongoing research. Many of the vascular benefits of exercise are thought to originate from the effect of elevated shear stress on the endothelium during exercise. Thijssen and colleagues have shown that conduit artery blood flow and shear rate incrementally increase with the intensity of exercise (as measured by VO_2 max) (Thijssen et

al. 2009). This increase in shear rate is a fundamental response to exercise and an important physiological stimulus, as laminar shear stress can both stimulate endothelial NO release and upregulate expression of endothelial nitric oxide synthase (Laughlin et al. 2008). Conversely, it can be argued that the maladaptive processes that occur in the vasculature of sedentary individuals are due to chronically low shear rates that are a consequence of inactivity. In this regard, low shear rates have been shown to stimulate ROS generation (Mohan et al. 2007), elevate expression of cell adhesion molecules (Wang and Liao 2004), reduce expression of intracellular antioxidants (Inoue et al. 1996), and cause release of pro-inflammatory endothelial microparticles (Vion et al. 2013).

To investigate the optimal intensity of exercise required to improve vascular function, Goto et al assigned healthy young men to mild (25% VO_2 max), medium (50% VO_2 max) or high intensity (75% VO_2 max) exercise regimens for 12 weeks and examined both endothelium-dependent and -independent vasodilation, as well as markers of oxidative stress (Goto et al. 2003). The medium intensity group showed increased acetylcholine-mediated vasodilation in the forearm microcirculation while no benefit was observed in the mild and high intensity groups. Shear rates generated in the mild intensity exercise group may have been inadequate to improve vascular function, but the lack of benefit in the high intensity training group was puzzling. Further study showed that markers of oxidative stress were increased in the high intensity exercise group, but not in the other groups. The authors speculated that a threshold of exercise intensity exists beyond which ROS generation overrides the scavenging capabilities of cellular antioxidant systems in the vasculature. This interpretation is further bolstered by a study from Bergholm and colleagues which showed that runners training at a relatively high intensity (70–80% of VO_2 max; 1 hour per day/4 days per week) for 12 weeks showed a decrease in circulating antioxidants during the training period in addition to a ~35% decrease in acetylcholine-mediated forearm vasodilation (Bergholm et al. 1999). Taken together, these studies along with others (Table 1) suggest that prolonged periods of intense physical training may cause excessive ROS generation to the point where overtraining becomes detrimental to vascular health.

Our group has investigated this concept in a unique set of athletes - elite women runners. In 1992, the American College of Sports Medicine proposed the term “female athlete triad” to describe the concurrent presence of amenorrhea, disordered eating and osteoporosis which was observed regularly in elite women runners. The presence of athletic amenorrhea in these young women results in a hormonal profile similar to that found in post-menopausal women, in which circulating estrogen levels are decreased from a hypothalamic origin. Reduced circulating estrogen would be expected to negatively affect endothelial NO production, similar to reductions reported in post-menopausal women who have heightened cardiovascular risk (Chambliss and Shaul 2002; Ihionkhan et al. 2002; Mendelsohn 2002; Rossi et al. 2008). Such an effect can be demonstrated by assessing brachial artery flow mediated vasodilation which is reduced both in post-menopausal women (Paradisi et al. 2004; Rossi et al. 2008) and in these young, athletic women who present with the athletic triad (Hoch et al. 2007; Hoch et al. 2009; Hoch et al. 2011b). This prompted Dr. Anne Zeni-Hoch, the lead author of these studies, to coin the phrase “female athlete tetrad” to emphasize the broader manifestation of this syndrome (Temme and Hoch 2013). A similar

reduction in conduit artery endothelial function was observed in professional ballerinas with the “female athlete triad” (Hoch et al. 2011a; Hoch et al. 2011b).

In follow-up studies, amenorrheic runners and professional dancers with reduced endothelial function were demonstrated to have nearly complete restoration of brachial flow mediated dilation after dietary supplementation with folic acid (10 mg/day) (Hoch et al. 2010; Hoch et al. 2011a) (Figure 3). The beneficial effects of folic acid on the vasculature are not completely understood, but folic acid likely increases NO bioavailability through either direct regeneration of essential cofactors required for endothelial nitric oxide synthase (Wever et al. 1997), or has direct antioxidant activity itself (Anderson et al. 1995; Doshi et al. 2001). These studies provide an important example of how extreme levels of exercise can modify the vascular phenotype of a healthy person to more closely mimic that of someone with coronary artery disease or its risk factors.

Resistance vs. Aerobic Exercise

The benefits of aerobic vs. resistance exercise are often compared with respect to fitness training. Substantial evidence supports the cardiovascular benefits of aerobic exercise, but resistance exercise is less well studied although generally considered safe and with cardiorespiratory benefit (Tanasescu et al. 2002). Just as with aerobic exercise described above, it is possible that there is a threshold beyond which isometric exercise could have detrimental effects on vascular health. Resistance exercise might be damaging through the associated elevations in arterial pressure. For example it has been shown that leg bench press exercise to 95% of maximal effort can transiently raise systolic blood pressure to values over 400 mmHg in trained weight lifters (MacDougall et al. 1985). This is alarming, because studies in animals have shown that transient increases in perfusion pressure of only 20–30mmHg can dramatically reduce coronary artery endothelial function for hours (Lamping and Dole 1987), or increase sensitivity to vasoconstrictor stimuli in skeletal muscle arterioles (Bagi et al. 2008).

We have extended these findings to leg bench press exercise in humans where a differential effect on endothelial function was observed after an acute bout of exertion in sedentary individuals compared to conditioned weight lifters. As shown in Figure 4, a single set of leg bench press reps significantly reduced brachial artery FMD in sedentary subjects; however, in the conditioned weightlifters FMD was maintained (Jurva et al. 2006). Cross trainers and runners were similarly protected from the reduction in FMD after isometric exertion (Phillips et al. 2011). Thus the same stressor may produce a different response in trained vs. untrained individuals.

The effects of isometric exercise on the microcirculation are more complex. Similar to the reduced FMD observed in the brachial artery after weight lifting, dilation to acetylcholine is reduced in adipose arterioles taken from gluteal fat pad biopsies of sedentary subjects after a bout of resistance exercise (Phillips et al. 2009). However, dose-dependent dilation to acetylcholine in microvessels taken from conditioned weight is maintained (Phillips et al. 2009). Unexpectedly, in the conditioned athletes the mediator of the dilation shifts from endothelial-derived NO to hydrogen peroxide released from the mitochondria of the

endothelial cell layer (Phillips et al. 2009). This is virtually identical to what is observed in the heart of patients with CAD. Studies from our laboratory have shown that the mechanism of coronary arteriolar flow-mediated dilation switches from NO to one that is mediated by mitochondrial-derived H₂O₂ released from the endothelium (Liu et al. 2003; Miura et al. 2003). This observation has been further extended to the peripheral circulation of individuals with CAD (Phillips et al. 2007), suggesting there may be consistent, systemic change in microvascular function in CAD, not just a change localized to the heart. It remains to be seen if other vascular beds respond similarly to exercise-induced hypertension.

The driving force for this change in vascular function in the athletes appears to be the increased blood pressure which results from weight lifting, as these results were recapitulated in preliminary studies using isolated vessels exposed only to high intraluminal pressure in the laboratory (Durand et al. 2013). Thus in both conditioned weight lifters and individuals with coronary artery disease, there is a dramatic change in the mechanism of dilation that involves a shift in the endothelial NO/ROS balance favoring a pro-oxidative state. Although this compensatory response in athletes and patients with heart disease preserves vasodilation, the long-term consequences of heightened vascular ROS in the face of reduced NO are uncertain and raise questions as to the benefit of such intense physical activity. Further research is needed to determine the time-course and threshold of exercise intensity needed for this mechanistic switch to occur. Such information will be important for optimizing and individualizing healthful exercise regimens for primary and secondary prevention of cardiovascular disease. In addition, for athletes such as elite women runners, impaired conduit artery FMD may have little effect at rest but could limit skeletal muscle blood flow at peak exercise. Supplements such as high dose folic acid have the potential to increase exercise induced dilation of conduit arteries to the limbs, and thus improve oxygen delivery and performance.

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Figure 1.

Reactive oxygen species contribute to endothelial dysfunction during extreme exercise. Intense bouts of exercise can significantly elevate systolic blood pressure and cause vascular inflammation, altering the vascular milieu to favor an oxidative environment. Prolonged exposure to a low concentration of NO and high concentration of ROS has the potential to induce vascular proliferation and cause endothelial dysfunction by similar mechanisms as those observed in overt cardiovascular disease. GPx (glutathione peroxidase); NO (nitric oxide); ROS (reactive oxygen species); SOD (superoxide dismutase); VSMC (vascular smooth muscle cell).

Figure 2.

Hypothetical exercise-hormesis curve plotting physical activity vs. cardiovascular risk.

Based on prospective studies and large observational studies, an optimal amount of exercise exists which maximizes cardiovascular benefit. Deviating to either extreme has the potential to increase cardiovascular risk. Adapted from La Gerche and Prior, 2007.

Figure 3.

Flow-mediated dilation changes after folic acid supplementation. Amenorrheic athletes received 4 weeks of supplementation, and eumenorrheic athletes received between 4 and 6 weeks of supplementation. Values are mean $\pm$ SD. *P values based on normal approximation to the Wilcoxon rank-sum test. Adapted from Hoch et al. 2010.

Figure 4.

Effect of exercise-induced hypertension induced by resistance exercise on endothelium dependent flow-mediated vasodilation (FMD) in conditioned weight-lifters (CWL) and non-conditioned weight-lifters (NWL). There was no difference in the brachial artery responses to flow before and after exercise in CWL, while there was a significant reduction in FMD after compared to before resistance exercise in NWL (* $p < 0.05$ compared to pre-exercise value NWL). There was no difference in the brachial artery responses to endothelium-independent nitroglycerin (NTG; 0.4 mg) between groups. Reprinted from Jurva et al. 2006.

Table 1

Reviewed articles that indicate intense exercise can be detrimental to vascular function. In general, the participants in these studies were in their early twenties and had no history of cardiovascular disease.

Study	Participants	Group Size	Type and Duration of Exercise	Method of Vascular Measurement	Key Findings
(Goto et al. 2003)	Healthy Japanese men	26	Cycle ergometry: 25, 50 or 75% VO_2 max 30 minute sessions, 5–7 days/week for 12 weeks	Strain gauge plethysmography: intrabrachial ACh infusion	Participants in the 75% VO_2 max group showed no improvement in forearm blood flow in response to ACh and had elevated markers of oxidative stress in the plasma.
(Bergholm et al. 1999)	Healthy men training for a marathon	9	Running: 70–80% VO_2 max 1 hour sessions, 4 days/week for 3 months	Strain gauge plethysmography: intrabrachial ACh infusion	Endothelium-dependent vasodilation in forearm vessels decreased by 32–35% during the training period. Circulating antioxidants in the plasma also decreased during training.
(Hoch et al. 2010)	Eumenorrheic and amenorrheic women runners	20	Runners: 20 miles/week for 12 months	Ultrasound: brachial artery flow mediated dilation	Brachial artery FMD was reduced in amenorrheic women runners. 4 weeks of folic acid supplementation normalized the FMD response in the amenorrheic group.
(Hoch et al. 2011a)	Elite women dancers	22	Professional ballet dancers	Ultrasound: brachial artery flow mediated dilation	Brachial artery FMD was reduced in 64% of ballet dancers studied. 4 weeks of folic acid supplementation significantly improved FMD in the group which showed abnormal FMD.
(Phillips et al. 2011)	Male runners, weight lifters, cross-trainers and sedentary subjects	53	Leg bench press: 2–3 sets of 6–8 repetitions of maximal exertion	Ultrasound: brachial artery flow mediated dilation	Brachial artery FMD was reduced in sedentary subjects after maximal exertion from weight lifting while no impairment of FMD was observed in weight lifters, runners, or cross-trainers.
(Phillips et al. 2009)	Male and female weight lifters and sedentary subjects	28	Leg bench press: 2–3 sets of 6–8 repetitions of maximal exertion	Cannulated vessel from gluteal fat biopsy: ACh-mediated vasodilation	Vasodilation to ACh in adipose resistance arterioles from sedentary subjects was reduced after a single weight lifting session. Vasodilation was maintained in arterioles from weight lifters; however the mediator of vasodilation switched from nitric oxide to mitochondrial-derived hydrogen peroxide.
(Durand et al. 2013)	Male and female weight lifters and sedentary subjects	19	None	Cannulated vessel from gluteal fat biopsy: ACh-mediated vasodilation	Exposing adipose resistance arterioles to an intraluminal pressure of 150 mmHg eliminated vasodilation in arterioles from sedentary subjects. Arterioles from weight lifters maintained vasodilation after high pressure exposure; however the mediator of vasodilation switched from nitric oxide to mitochondrial-derived hydrogen peroxide.