

Article Review

Exercise and vascular adaptation in asymptomatic humans

Daniel J. Green^{1,2}, Angela Spence², John R. Halliwill³, N. Timothy Cable¹ and Dick H. J. Thijssen^{1,4}¹Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, UK²School of Sport Science, Exercise and Health, The University of Western Australia, Crawley, Perth, Western Australia, Australia³Department of Human Physiology, University of Oregon, Eugene, OR, USA⁴Department of Physiology, Radboud University Nijmegen Medical Centre, The Netherlands

Beneficial effects of exercise training on the vasculature have been consistently reported in subjects with cardiovascular risk factors or disease, whereas studies in apparently healthy subjects have been less uniform. In this review, we examine evidence pertaining to the impact of exercise training on conduit and resistance vessel function and structure in asymptomatic subjects. Studies of arterial function *in vivo* have mainly focused on the endothelial nitric oxide dilator system, which has generally been shown to improve following training. Some evidence suggests that the magnitude of benefit depends upon the intensity or volume of training and the relative impact of exercise on upregulation of dilator pathways *versus* effects of inflammation and/or oxidation. Favourable effects of training on autonomic balance, baroreflex function and brain-stem modulation of sympathetic control have been reported, but there is also evidence that basal vasoconstrictor tone increases as a result of training such that improvements in intrinsic vasodilator function and arterial remodelling are counterbalanced at rest. Studies of compliance suggest increases in both the arterial and the venous sides of the circulation, particularly in older subjects. In terms of mechanisms, shear stress appears to be a key signal to improvement in vascular function, whilst increases in pulse pressure and associated haemodynamics during bouts of exercise may transduce vascular adaptation, even in vascular beds which are distant from the active muscle. Different exercise modalities are associated with idiosyncratic patterns of blood flow and shear stress, and this may have some impact on the magnitude of exercise training effects on arterial function and remodelling. Other studies support the theory that there may be different time course effects of training on specific vasodilator and constrictor pathways. A new era of understanding of the direct impacts of exercise and training on the vasculature is evolving, and future studies will benefit greatly from technological advances which allow direct characterization of arterial function and structure.

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Corresponding author D. J. Green: Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Henry Cotton Campus, 15-21 Webster Street, Liverpool L3 2ET, UK. Email: d.j.green@ljmu.ac.uk

Heart disease and stroke are the major causes of death in middle- and high-income countries. Disease of conduit arteries underlies much of this global burden, whilst dysfunction of resistance arteries and smaller arterioles is associated with hypertension and the disabling manifestations of microvascular disease. Exercise decreases cardiovascular risk, and the benefit in both primary and secondary prevention settings may be greater than 30% (Thijssen *et al.* 2010b). Significant risk reduction is apparent even in subjects receiving optimal contemporary medical and interventional management.

Whilst this strongly infers an effect of exercise on arterial health, the mechanisms responsible are not fully understood, and it appears that the beneficial effects of exercise on traditional risk factors may only explain half of the risk reduction (Mora *et al.* 2007). It is possible that direct effects of exercise on the vessel wall may account for some of the remaining 'risk factor gap' (Green *et al.* 2008a), although other explanations exist (Joyner & Green, 2009). Whether the mechanisms responsible for the benefits of exercise training are primary, or mediated secondarily through modulation of traditional risk factors, methods

now exist which enable direct assessment of adaptation in arterial function and structure. Indeed, direct measures of conduit artery function provide prognostic information which equals or exceeds that available from assessment of traditional cardiovascular risk factors (e.g. Yeboah *et al.* 2009). Previous reviews have emphasized the impact of exercise training on the vasculature of subjects with existing cardiovascular disease and/or risk factors (Maiorana *et al.* 2003; Green *et al.* 2004; Moyna & Thompson, 2004), so we have focused this review on changes observed in healthy subjects and discussion of some of the mechanisms involved.

Physiological adaptations to exercise can depend upon the intensity of exercise as well as its modality, duration and frequency. Most studies have been performed using 'aerobic' or 'endurance' types of exercise, which involve large muscle group repetitive dynamic contractions (e.g. walking, cycling or running), associated with systemic changes in pulse pressure and heart rate, which generate recurrent changes in haemodynamics and arterial shear stress. Other studies have incorporated small muscle group exercises (e.g. handgrip exercise), which provide insight into localized effects of exercise, which are less dependent upon central regulatory or neural changes. Still other studies have adopted 'resistance' exercise modalities, which may not only induce different skeletal and cardiac muscle adaptations (Naylor *et al.* 2008), but may also involve different haemodynamic signals (Thijssen *et al.* 2009a). The impact of 'exercise' is therefore nuanced and multifaceted. In the present review, we have focused on recent conceptual issues which may shed some light on mechanisms and potentially explain some disparity in the literature pertaining to adaptations in healthy subjects. Where necessary, we have highlighted relevant aspects of the training stimulus in the present review, whilst elsewhere the reader is referred to longer reviews that contain more descriptive detail of specific studies and training effects (Maiorana *et al.* 2003; Green *et al.* 2004; Moyna & Thompson, 2004; Thijssen *et al.* 2010b).

Exercise training and vasodilator function

Due to its anti-atherogenic roles, the most commonly interrogated vasodilator pathway has been the nitric oxide (NO) vasodilator system (Green *et al.* 2004). The function of this pathway can be assayed in resistance vessels by intra-arterial infusion of receptor agonists, such as acetylcholine, before and after training (Vallance *et al.* 1989), with NO sensitivity of vascular smooth muscle interrogated using sodium nitroprusside or glyceryl trinitrate. In some of these experiments, NO antagonists, such as N^G -monomethyl-L-arginine, have also been infused before and after training to determine the impact of exercise on basal NO function (Goto *et al.* 2003). A conceptually similar approach has also been adopted to assess

microvascular function, using laser Doppler assessments in the skin during agonist or antagonist administration via microdialysis or iontophoresis (Cracowski *et al.* 2006; Black *et al.* 2008).

In conduit arteries, function has typically been examined using the approach popularized by Celermajer *et al.* (1992), in which endothelium-dependent vasodilator function is assessed by high-resolution ultrasound following an increase in blood flow, which triggers flow and shear stress-mediated vasodilatation (FMD). Sublingual glyceryl trinitrate is used in such experiments to assess smooth muscle NO-mediated relaxation. Assessment of FMD and glyceryl trinitrate-induced dilatation has the advantage of not requiring arterial cannulation, but suffers from a lack of direct delivery of known endothelial and smooth muscle vasoactive drug concentrations and lack of normalization of the shear stress stimulus between individuals. It is also important to emphasize that, whilst FMD provides a test of conduit endothelial function, it only examines pathways stimulated by shear stress, and possibly arterial and transmural pressure change. It is likely that exercise training induces changes in many signaling pathways and vasodilator mechanisms other than that induced by FMD. In this review, studies of FMD are a focus, due in part to the lack of data relating to alternative vasodilator pathways and tests.

Does exercise training enhance vasodilator function in healthy asymptomatic humans? The overwhelming majority of studies undertaken in subjects with cardiovascular diseases or risk factors report that exercise training improves vasodilator function of resistance or conduit arteries (Thijssen *et al.* 2010b). Most, but not all, of these have suggested that the benefit is limited to the function of the endothelium; smooth muscle function is usually reported to be unaltered. Studies which have suggested improvement in smooth muscle function have typically been undertaken in patients with more severe disease, suggesting a hierarchy of dysfunction and amelioration which begins with the endothelium and migrates to the rest of the vessel wall (for reviews see Maiorana *et al.* 2003; Green *et al.* 2004; Thijssen *et al.* 2010b). Collectively, these data suggest that vascular function is amenable to improvement, despite its initial impaired status, in subjects at known or increased risk of cardiovascular disease.

The findings in healthy asymptomatic subjects with presumably normal endothelial function are less consistent (Green *et al.* 2004). Whilst fewer studies have been completed in such subjects, nearly half of these have not observed adaptation in NO agonist responses or FMD (Thijssen *et al.* 2010b). The difference between studies performed in symptomatic subjects *versus* those in healthy individuals is apparent regardless of whether the training

involved localized or large muscle systemic exercise, even though these forms of exercise induce different shear stress patterns and reflex responses (Green *et al.* 2005; Thijssen *et al.* 2009a). By way of example, studies of patients with heart failure (Maiorana *et al.* 2000), coronary artery disease (Walsh *et al.* 2003) and type 2 diabetes (Maiorana *et al.* 2001a) all resulted in enhanced resistance vessel and/or conduit artery endothelial function, whereas an identical exercise regime failed to induce improvement in a group of apparently healthy middle-aged subjects (Maiorana *et al.* 2001b; Fig. 1), suggesting that it may be difficult to enhance 'normal' function in healthy subjects (Maiorana *et al.* 2003; Green *et al.* 2004).

Those studies which have demonstrated enhancement in vasodilator function in healthy volunteers suggest that a moderate-to-higher load (i.e. intensity and/or frequency, duration) of training may be required to impact endothelial function in healthy asymptomatic subjects who demonstrate preserved endothelial function *a priori* (Green *et al.* 2004). This hypothesis is supported by the data of Goto *et al.* (2003) and others (Bergholm *et al.* 1999; Dawson *et al.* 2008), which suggest that low-to-moderate exercise loads may be associated with improvement in endothelial function, whereas more intense or higher load training may be associated with oxidative stress-induced amelioration of such improvement. Other studies have demonstrated that exercise modality modulates the shear stress pattern presented as a stimulus to endothelial adaptation in various vascular beds (Green *et al.* 2005; Thijssen *et al.* 2009a; Fig. 2). Hence, differences in baseline vascular function or the nature of the exercise stimulus used in studies of healthy subjects may account for some of the variability in outcomes.

Recently, another possible explanation has emerged. Informed by the studies of Laughlin and co-workers in animals (Laughlin, 1995; Jasperse & Laughlin, 2006), we examined the time course of change in conduit artery endothelial function in healthy young subjects (Tinken *et al.* 2008, 2010). Whilst FMD was initially enhanced, it subsequently declined to pretraining levels, suggesting that modification of vascular function occurs rapidly (Fig. 3) and may then be superseded by changes in arterial structure or in other vasodilator pathways. Hence, previous studies in healthy subjects may have missed adaptations in endothelial function, as these can occur rapidly and may then subside. This finding raises questions regarding the time course of modulation in vascular function in both health and disease. It is important to note that these observations pertaining to the time course of arterial adaptation in humans are specific to FMD, and other studies will be necessary to address the question of whether other functional adaptations are transient.

The studies described above involved measurement of resistance vessel or conduit artery responses. The question of whether exercise training enhances microvascular

endothelial function in healthy asymptomatic subjects was also recently addressed (Black *et al.* 2008). Skin vasodilator responses were lower in untrained older subjects than healthy younger volunteers and endurance-trained veteran athletes. Exercise training enhanced both ACh-mediated and local heating-induced vasodilator function in the older initially sedentary subjects (Fig. 4). Whilst these findings are specific to skin microvessels, they reinforce the landmark finding that exercise training enhances coronary microvascular responses, assessed using the flow response to intracoronary adenosine infusion (Hambrecht *et al.* 2000).

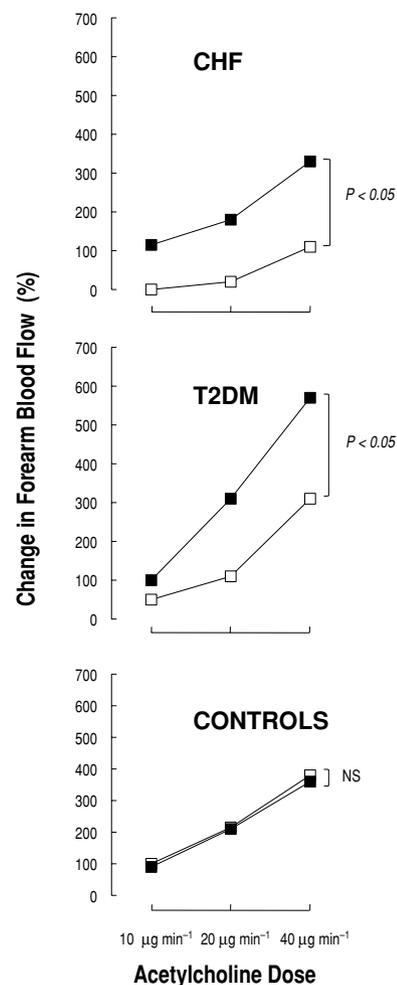


Figure 1. Impact of exercise training on resistance vessel endothelial function in disease and health

Identical exercise training regimes induced improvement (open symbols pretraining, closed symbols post-training) in NO-mediated acetylcholine-induced vasodilator function in subjects with heart failure (CHF), type 2 diabetes (T2DM) and other risk factors, but not in asymptomatic age-matched control subjects. This may imply that endothelial function is amenable to improvement when impaired *a priori*, whereas supra-normalization is more difficult to induce. Alternatively, the time course or magnitude of adaptation may differ in healthy subjects *versus* those with cardiovascular disease and risk factors. Data are derived from Maiorana *et al.* (2000), (2001a,b).

In summary, exercise training can improve vasodilator function in human conduit, resistance and microvessels. There are, however, numerous examples of studies in healthy humans that have not demonstrated training adaptations. Several reasons for this discordance exist, including idiosyncratic differences between groups in the time course of vascular adaptation and the *a priori* status of vascular function in different groups of apparently healthy subjects. Differential effects of the exercise training stimulus may also be apparent, with some studies indicating that resistance training can induce remodelling without changes in arterial function (Rakobowchuk *et al.* 2005b).

Acute exercise, exercise training and vasodilator function: role of shear stress. Hambrecht *et al.* (2003) produced evidence that shear stress may be an important mechanism in transducing changes in endothelial vasodilator function following exercise training in humans by demonstrating

that both *in vitro* and *in vivo* enhancement in endothelial function in the internal mammary artery were associated with increased endothelium-derived NO synthase shear-related protein expression. This paper, along with animal data implicating shear stress as an important transduction stimulus (see Laughlin *et al.* 2008), raised important questions about the nature and magnitude of shear stress responses to acute bouts of exercise in humans.

At the same time, it was observed that lower limb exercise training provokes upper limb vascular adaptation, prompting the suggestion that exercise training induces generalized systemic effects on endothelial function (Linke *et al.* 2001; Green *et al.* 2008b). We therefore examined the acute impact of different exercise modalities on upper limb blood flow and observed different patterns of flow and shear during leg *versus* handgrip exercise, including retrograde diastolic flows during cycling (Green *et al.* 2002c, 2005). These different flow and shear patterns

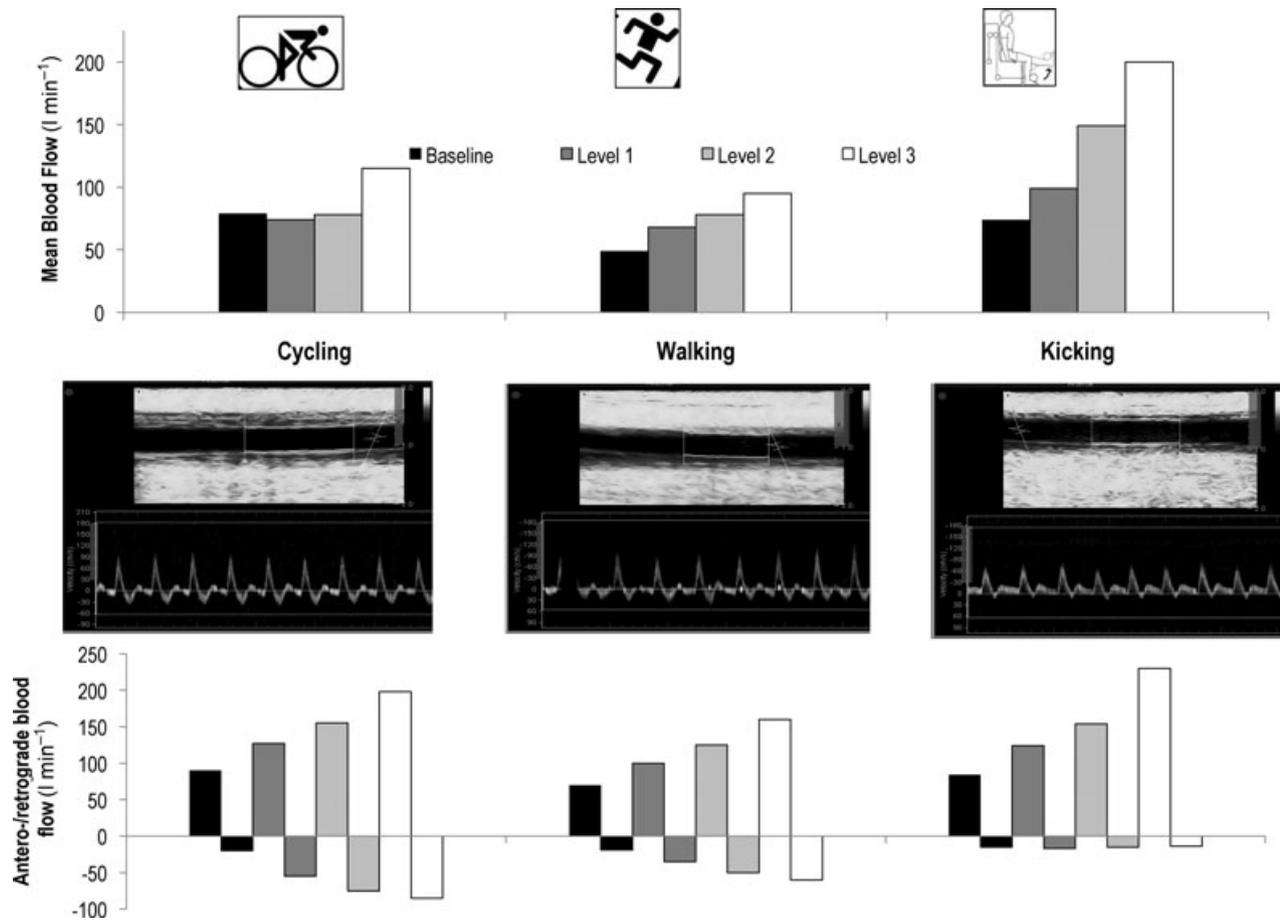


Figure 2. Impact of exercise modality on arterial haemodynamics

Shear stress, a potent stimulus to adaptation in arterial function and structure, may differ with different exercise modalities. Large muscle group rhythmic and dynamic exercise, such as walking, cycling and running, induces similar patterns of shear stress in non-active vessel beds (e.g. the upper limbs), involving increases in both antero- and retrograde flow and shear. Handgrip and leg kicking exercise are not associated with this pattern. See Thijssen *et al.* (2009a) and Green *et al.* (2005).

may have implications for production of endothelium-derived substances, such as NO (Green *et al.* 2002*b*, 2005), and different patterns of flow are associated with different modalities of exercise (Thijssen *et al.* 2009*a*; Fig. 2).

To examine the potential roles of pulse pressure and heart rate on shear stress-induced production of endothelium-derived NO, heart rate at rest was increased in patients with implanted pacemakers to levels they exhibited during incremental cycle exercise. In the absence of increases in pulse pressure, increased heart rate was not associated with enhanced NO function, determined using intra-arterial infusion of a NO blocker (Green *et al.* 2002*a,b*; Fig. 5). This, along with findings regarding retrograde arterial flow and shear (Green *et al.* 2002*b*, 2005), led to an investigation of the impact of the pattern of blood flow on vascular function. Using acute shear stress-modulating interventions, such as forearm heating, handgrip exercise and cycle ergometry, brachial artery shear stress was modified simultaneously in both arms, with unilateral cuff inflation to manipulate shear stress patterns within subjects (Tinken *et al.* 2009). These experiments suggested that increases in anterograde flow and shear may be important modulators of the acute effect of exercise on endothelial function. There is also some evidence that retrograde shear may decrease this beneficial effect (Thijssen *et al.* 2009*b*; Fig. 6).

More recently, to examine the suggestion that shear is a key mechanism responsible for enhanced endothelium-mediated vasodilator function following exercise training (Hambrecht *et al.* 2003), subjects performed a bilateral handgrip training programme previously shown to induce changes in vascular function and structure in humans (Tinken *et al.* 2009, 2010). During training sessions, a cuff was placed around one arm to produce a unilateral decrease in the blood flow and shear stress associated with each exercise bout in that limb (by >50%; see Fig. 6; Tinken *et al.* 2009). Despite similar training effects on forearm volume, girth and strength, vasodilator function improved only in the limb exposed to increases in shear stress during the training bouts, leading to the conclusion that shear stress is a principal physiological stimulus to the vascular adaptation associated with exercise training *in vivo* (Fig. 3). In order to confirm the importance of shear stress, independent of the complex stimulus of exercise, a subsequent study induced repeated episodic increases in shear stress at rest, using bilateral forearm heating in the absence of exercise. The experimental approach involved cuffing one arm during the heating bouts to provide a within-subjects experimental manipulation of shear. Only the limb exposed to the greater change in blood flow and shear during heating bouts, that is, the forearm that was not exposed to cuffing, demonstrated improvement in NO-mediated vasodilator responses (Green *et al.* 2010*a*; Naylor *et al.* 2010; Fig. 7).

Summary: exercise training and vasodilator function. It appears that changes in shear stress which are associated with acute bouts of exercise provide a potent stimulus to vasodilator adaptation to training *in vivo*. Repeated shear stress stimulation and consequent adaptation in vasodilator pathways, associated with some forms of exercise training, could therefore explain some of the direct effects of exercise on the vasculature. The magnitude of shear stress change induced by exercise, as well as the precise pattern of flow and shear, may therefore have implications for the magnitude of adaptation observed with training and may explain some of the diverse effects of different exercise modalities and intensities in healthy humans (Wisloff *et al.* 2007).

Exercise training and vasoconstrictor function

The question of whether neutrally mediated vasoconstriction is modified by exercise training is complex, and various approaches to this question have produced contradictory results. On the one hand, there is strong evidence that heart rate variability, a measure of autonomic balance which predicts cardiovascular mortality, is improved by exercise training (Rennie *et al.* 2003; Wichterle *et al.* 2004; Buchheit *et al.* 2005), and other studies suggest that noradrenaline levels diminish following training (Galbo, 1983). In keeping with these findings, there is evidence that training ameliorates the effect of ageing on baroreflex function (Monahan *et al.*

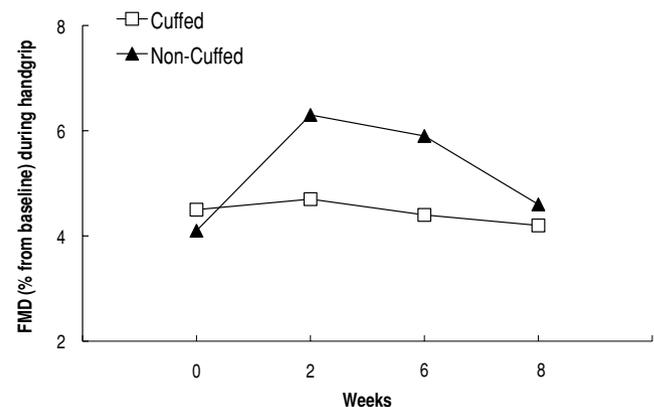


Figure 3. Time course of adaptation in arterial function in response to exercise training and the impact of shear stress modulation on this response

Flow-mediated dilatation (FMD), an index of endothelial function, adapts rapidly to training and then returns towards baseline levels. These adaptations may be superseded by other functional changes or structural arterial remodelling (see Tinken *et al.* 2008; Tinken *et al.* 2010). When the shear stress response to each bout of exercise was ameliorated by inflation of a proximal pressure cuff, functional adaptations were not apparent. These studies suggest that repeated increases in shear stress are obligatory for adaptation of conduit arterial function in response to exercise training.

2000), an effect which may be related to enhanced arterial vasodilator function, arterial distensibility and/or signal transduction in barosensitive zones (Joyner & Green, 2009). In addition, muscle sympathetic nerve activity may decrease as a result of exercise training (Ray & Hume, 1998) or in subjects with elevated sympathetic nervous system activity *a priori* (Roveda *et al.* 2003; Fraga *et al.* 2007). Finally, it has been suggested that repeated bouts of exercise and associated cyclic activation of brainstem centres, such as the rostral ventrolateral medulla, may modulate central sympathetic output and, conceivably, sympathetic nervous system-mediated vasoconstriction (Mueller, 2010). These studies suggest that sympathetic nerve-mediated vasoconstrictor tone may decrease as a result of exercise training in humans.

However, there is also evidence to the contrary. Studies performed in healthy subjects suggest that

muscle sympathetic nerve activity does not change with training (Svedenhag *et al.* 1984; Roveda *et al.* 2003), and noradrenaline spillover may also be similar following training when expressed in relative terms (Rowell, 1993). In addition, α -adrenoceptor blockade revealed an increased level of basal sympathetic vasoconstrictor tone following endurance training in healthy volunteers (Sugawara *et al.* 2007; Fig. 8), consistent with other evidence of elevated basal sympathetic tone following training (Alvarez *et al.* 2005). Despite this apparent increase in resting sympathetic tone, basal blood flows are not decreased by training, suggesting that increased vasodilator function or arterial remodelling following training may be offset by elevated sympathetic tone, with the result that resting blood flows and arterial diameters remain unchanged. In keeping with this proposal, Haskell *et al.* (1993) have also reported, in coronary arteries,

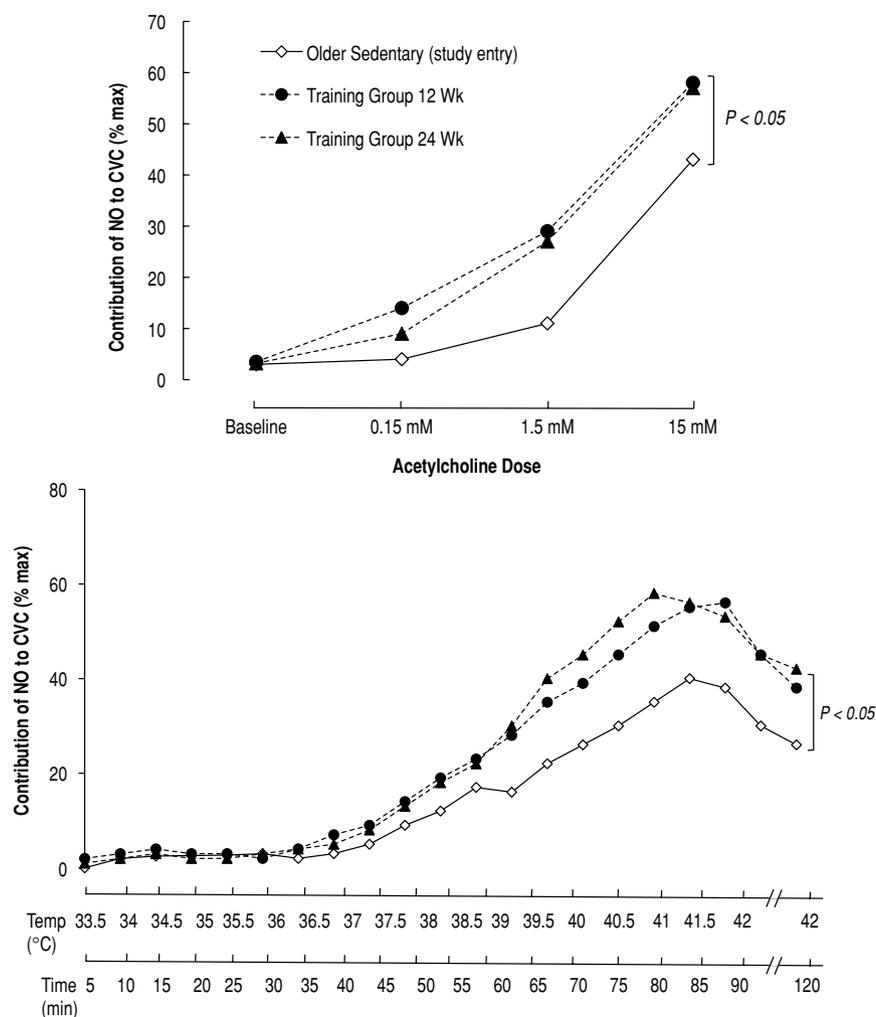


Figure 4. Microvascular adaptation to exercise training

Exercise training in older healthy subjects increases nitric oxide-mediated vasodilatation (CVC, cutaneous vascular conductance) in response to acetylcholine or delivery by microdialysis and also a gradual local heating stimulus. See Black *et al.* (2008).

evidence consistent with elevated basal vasoconstriction tone in trained subjects who possessed structurally enlarged arteries.

Apart from sympathetic nerve-mediated vasoconstriction, there are several humoral vasoconstrictors which may be modulated by exercise training. Exercise training in patients with cardiovascular disease has beneficial effects on endothelin-1 (ET-1) and angiotensin II pathways (Adams *et al.* 2005), suppresses circulating concentrations

of angiotensin II (Braith *et al.* 1999) and lowers plasma concentrations of ET-1 (Kubanek *et al.* 2006; Maeda *et al.* 2009). These findings are replicated in animals, as exercise training diminishes the aortic and cerebellar sensitivity to ET-1 (Latorre *et al.* 2002). However, another study found no relation between ET-1 levels and the contribution of ET-1 to baseline vascular tone (Thijssen *et al.* 2008a), questioning the clinical relevance of a change in ET-1 levels. Whilst no previous study has examined the impact of exercise training on the contribution of ET-1

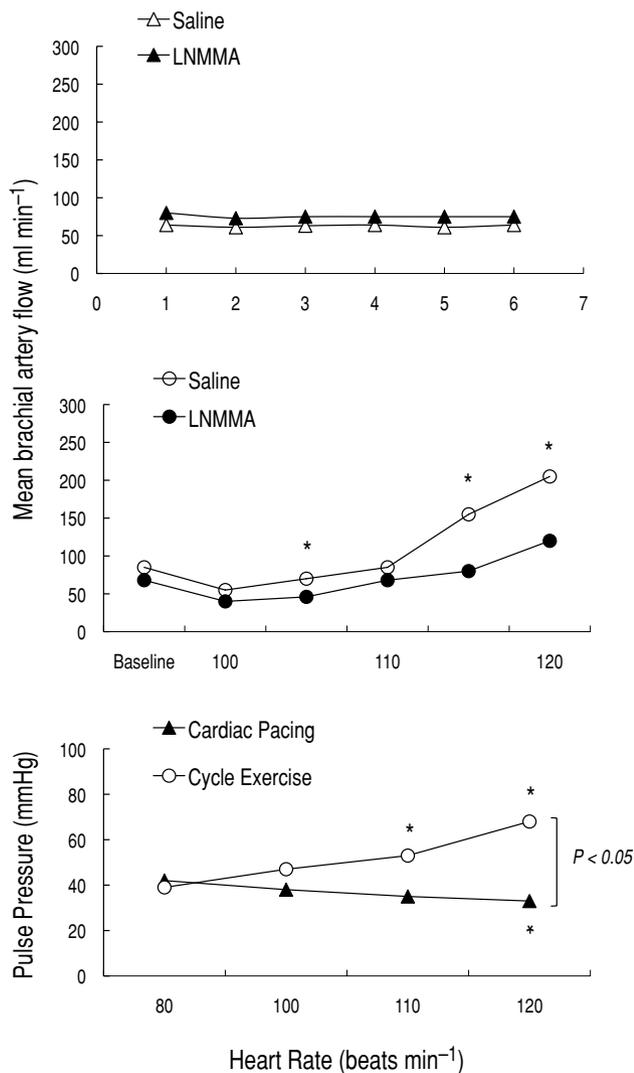


Figure 5. Acute impacts of pulse pressure and pulsatility on endothelial function

Cycle ergometer exercise is associated with increased pulse pressure in humans (bottom panel), whereas increasing heart rate to similar levels in resting subjects by dialling up a pacemaker does not widen pulse pressure (bottom panel). Increases in pulse pressure during cycling were associated with increased production of endothelium-derived nitric oxide in the forearms, whereas pacing at similar heart rates was not associated with increased NO bioactivity. This suggests that pulse pressure, rather than pulsatility, may transduce endothelial adaptation. See Green *et al.* (2002a,b).

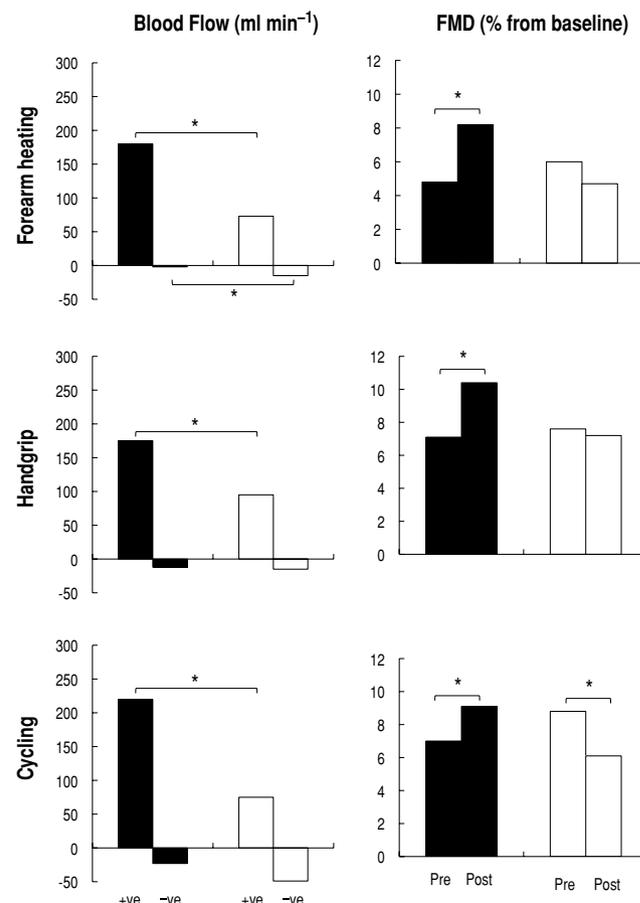


Figure 6. Acute impact of different shear stress patterns on the endothelium-dependent flow-mediated responses

Forearm heating, handgrip exercise and cycle ergometer exercise all increased anterograde blood flow (denoted +ve) through the brachial artery, and such increases were associated with enhanced flow-mediated dilatation (FMD), an endothelium-dependent vasodilator response (filled bars in right panel; see Tinken *et al.* (2009). When a cuff was applied to the contralateral limb during each of these manipulations (open bars), anterograde flow and shear stress were attenuated (left panel) and FMD did not increase (right panel). During cycle ergometry in the cuffed arm, an increase in retrograde flow (denoted -ve) was associated with decreased FMD (see bottom right panel). These findings suggest that anterograde flow acutely enhances and retrograde flow acutely decreases endothelial function *in vivo*. The latter finding was supported by subsequent studies involving stepwise increases in retrograde flow (Thijssen *et al.* 2009b).

to vascular tone in healthy asymptomatic subjects, recent experiments suggest a role for ET-1, determined using intra-arterial infusion of endothelin-receptor blockers, in the age-related increase in vascular tone in both the lower (Thijssen *et al.* 2007b) and upper extremities (Van Guilder *et al.* 2007). Moreover, training partly reversed elevated ET-1-mediated vascular tone in older men (Thijssen *et al.* 2007b; Van Guilder *et al.* 2007).

Regarding the angiotensin II pathway, 6 weeks of training was associated with a lower angiotensin II-induced pulmonary vasoconstriction in healthy rats (Kashimura *et al.* 1995). In humans, only one study to our knowledge has examined potential differences in the regulation of vascular tone by angiotensin II. Intra-arterial infusion of angiotensin II revealed similar responses between healthy athletic and sedentary men (Kingwell *et al.* 1996). Although other vasoconstrictors have been identified (thromboxane A₂ and prostaglandin H₂), the impact of exercise on these is relatively unexplored (Thijssen *et al.* 2008a).

In summary, despite the limited attention paid to ET-1 and angiotensin II, these vasoconstrictors appear to play a role in the physiological regulation of vascular tone and structure, whilst they also have direct effects on the sympathetic nervous system. The limited number of longitudinal training studies in healthy humans suggest a direct effect of exercise training on vasoconstrictor pathways.

Exercise training and arterial calibre

Measures of vasodilator capacity, such as peak blood flow responses or peak diameter changes in response to ischaemia or ischaemic exercise (Sinoway *et al.* 1986; Green *et al.* 1996; Rakobowchuk *et al.* 2005b; Naylor *et al.* 2006), have been used to assess the extent of arterial remodelling of resistance vessel beds and conduit arteries *in vivo*, based on the assumption that it is necessary to dilate the vessel maximally in order to ascertain the real magnitude of remodelling, free of competing effects, such as sympathetic

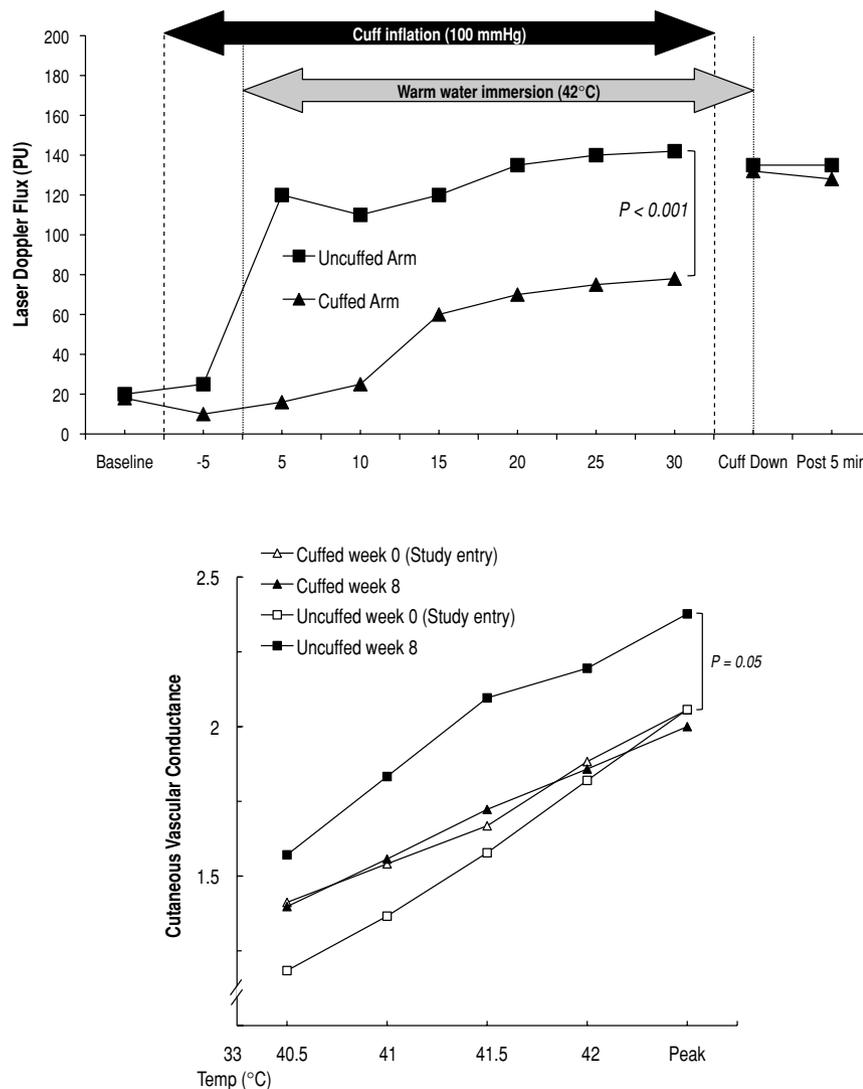


Figure 7. Impact of shear stress on microvascular adaptation in humans

Forearm heating-induced increases in microvascular blood flow (or laser Doppler flux) were attenuated in the contralateral heated limb by proximal pressure cuff inflation (top panel). When nitric oxide-mediated skin blood flow responses were assessed after 4 and 8 weeks of repeated heat exposure, adaptations in cutaneous vascular conductance were observed only in the limb exposed to increased blood flow/shear stress, i.e. the uncuffed limb (Green *et al.* 2010a). These data suggest an important role for shear stress in microvascular adaptation to exercise training in humans. PU, Perfusion Units.

tone (Takeshita & Mark, 1980; Sinoway *et al.* 1986, 1987).

Differences in peak vasodilator capacity of peripheral arterial beds measured in this way have been consistently reported between athletes and control subjects, but such cross-sectional comparisons may be influenced by scaling issues (Thijssen *et al.* 2008*b*; Hopkins *et al.* 2009). Longitudinal training studies involving small muscle groups have generally induced increases in peak vasodilator responses, suggesting collective luminal expansion of resistance arteries (Sinoway *et al.* 1986; Green *et al.* 1996; Rakobowchuk *et al.* 2005*b*; Naylor *et al.* 2006). These findings are intrinsic to the trained resistance arteries, do not involve sympathetic withdrawal (Sinoway *et al.* 1986, 1987) and are unlikely to be due to increased capillary density (Brown *et al.* 1976; Hudliká *et al.* 1977). There are a few studies which suggest that lower limb exercise training may be capable of enhancing peak vasodilator capacity of the upper limbs (Silber *et al.* 1991; Maiorana *et al.* 2000), suggesting a systemic effect of exercise on arterial remodelling in keeping with the concept of enhanced vascular capacitance described by Clausen (1977).

As with the findings in resistance arteries, resting coronary and peripheral conduit arterial diameters have been reported to be larger in athletes than in control subjects (Zeppilli *et al.* 1995; Huonker *et al.* 2003; Thijssen *et al.* 2010*b*), although few of these studies corrected for scaling. Nonetheless, longitudinal training studies undertaken using within-subjects designs suggest that conduit artery diameter is enlarged in trained limbs (Dinunno *et al.* 2001; Miyachi *et al.* 2001; Naylor *et al.* 2006) and that the effect is regional, rather than central or reflex in nature. Studies in which training has involved one leg, which illustrate changes in the trained but not the contralateral untrained extremity, imply that localized effects on haemodynamics in the conduit arteries, rather than systemic arterial pressure effects (which would logically affect both limbs), may be responsible (Miyachi *et al.* 2001; Thijssen *et al.* 2010*b*). In this context, it is well established that localized changes in shear stress can induce endothelium-dependent arterial remodelling (Langille & O'Donnell, 1986).

Importantly, Haskell *et al.* (1993) demonstrated that basal sympathetic tone may be higher in structurally enlarged coronary arteries at rest, when metabolic demand is low. They observed larger epicardial arterial diameters in athletes relative to control subjects, but only after dilating the arteries to near maximum. Generally, studies of the coronary circulation indicate that exercise is associated with enlargement of both resistance and conduit levels of the vasculature (Haskell *et al.* 1993; Hambrecht *et al.* 2000; Thijssen *et al.* 2010*b*), although the data are less consistent than for peripheral arteries, and there are fewer studies

due to the invasive nature of the experimental methods (Thijssen *et al.* 2010*b*).

The studies described above provide compelling evidence that exercise induces changes in the size of both conduit and resistance arteries and that the effects can perhaps be systemic if the haemodynamic stimulus is sufficiently large and prolonged. Whilst most of these studies involved aerobic or endurance exercise modalities, there is also evidence that some forms of resistance training can induce arterial remodelling of conduit and resistance arteries in healthy subjects (Maiorana *et al.* 2001*b*; Rakobowchuk *et al.* 2005*b*). A role for shear stress is suggested by animal data and recent human work which indicates that changes in vasodilator capacity are not evident in muscles that have exercised in the absence of hyperaemia (Laughlin *et al.* 2008; Tinken *et al.* 2008, 2010; Green *et al.* 2010*a*).

Exercise training and changes in arterial wall thickness

Studies of arterial wall thickness were originally performed in the carotid arteries, where increased intima–

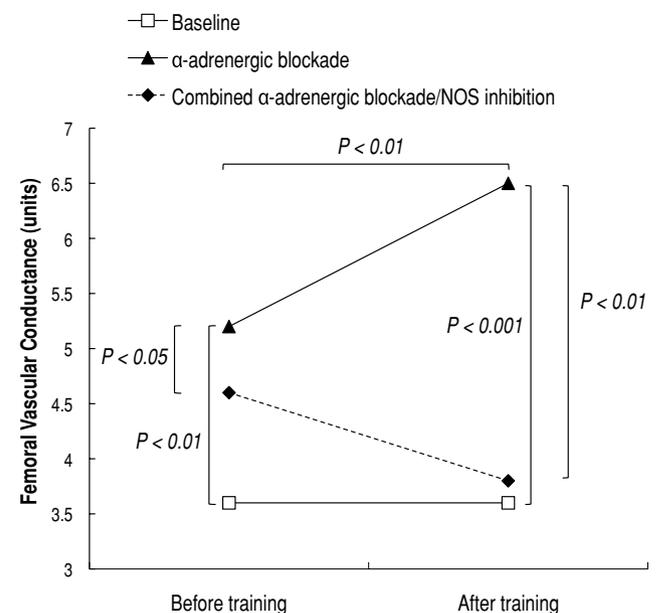


Figure 8. Role of adrenergic vasoconstrictor and nitric oxide vasodilator function in the exercise training-mediated change in resting femoral artery blood flow

Exercise training did not modify resting or baseline leg blood flow or conductance. Sympathetic control of the vasculature was augmented following training, as indicated by the increased impact of α -adrenoceptor blockade. Nitric oxide inhibition was also augmented following training. These data suggest that exercise training is associated with elevated resting vasodilator tone, which is offset, at rest, by elevated sympathetic vasoconstriction. See Sugawara *et al.* (2007).

medial thickening is considered an index of preclinical atherosclerosis. More recently, the impact of exercise has been assessed in other large arteries of the upper and lower limbs, to determine the impact of training on physiological remodelling (Seals *et al.* 2008). It appears that, whilst training does not typically impact upon carotid artery thickness or diameter (Tanaka *et al.* 2002; Moreau *et al.* 2006), it can influence the thickness of femoral (Dinenno *et al.* 2001), brachial and popliteal arteries (Green *et al.* 2010b). Exercise training in older subjects induced remodelling of conduit arteries, leading to decreased wall thickness and increased lumen diameters, with consequent decrease in the wall-to-lumen ratio (Green *et al.* 2010b). These findings suggest that endurance training has a larger effect on wall thickness in 'muscular' arteries than in larger, more 'elastic' arteries (Moreau *et al.* 2002; Tanaka *et al.* 2002). Such changes in wall thickness and wall-to-lumen ratio may take time, since 8 weeks of training does not induce significant changes in wall thickness (Thijssen *et al.* 2007a).

There have been few studies of the impact of different exercise modalities on arterial wall thickness, with findings in healthy subjects suggesting that resistance training may not modulate wall thickness (Rakobowchuk *et al.* 2005a; Seals *et al.* 2008), whilst resistive training in patients with heart failure may induce some changes (Maiorana *et al.* 2010). Interestingly, a recent study found that 'vibration' exercise is capable, at least in part, of preventing the increase in artery wall thickness evident in healthy humans exposed to prolonged bed rest (van Duijnhoven *et al.* 2010).

Exercise training and arterial remodelling: summary. It is tempting to speculate that changes in wall thickness and lumen diameter may reflect adaptations consistent with the Law of Laplace, around normalization of wall stress. However, the impact of changes in wall-to-lumen ratio on vascular responsiveness is also a consideration, with Folkow pointing out as far back as the 1950s that such changes can have implications for hypertension (Folkow *et al.* 1958). Exercise training may remodel arteries in a way that decreases wall stress, blood pressure and the risk for atherothrombotic infarction.

Exercise training and arterial compliance

The majority of studies performed in subjects with cardiovascular diseases or risk factors indicate that exercise training improves arterial compliance, independent of the duration of the intervention or the vessel studied (O'Rourke & Hashimoto, 2008; Seals *et al.* 2008). Potential mechanisms include changes in intrinsic elastic properties of the artery wall (structural determinants) and/or vasomotor tone of smooth muscle cells (functional determinant). The latter may relate to changes in

vasoconstrictor and dilator pathways described above. Collectively, these data suggest that vascular compliance can be improved in subjects at known or increased risk of cardiovascular disease.

In healthy asymptomatic middle-aged and older men, endurance-trained subjects demonstrated higher arterial compliance than their inactive peers, whilst sedentary, recreationally active and endurance-trained young subjects exhibited no difference in arterial compliance (Tanaka *et al.* 2000; Gates *et al.* 2003). Other studies found no impact of aerobic exercise training (Rakobowchuk *et al.* 2008) on central or carotid arterial compliance in young asymptomatic subjects, but enhanced compliance in exercise-trained middle-aged and older subjects (Tanaka *et al.* 2000; Maeda *et al.* 2009) who demonstrate impaired arterial compliance *a priori*. These data suggest no impact of aerobic endurance exercise on arterial compliance in young people, but possible improvement in arterial compliance in inactive middle-aged and older men.

Resistance training impacts arterial compliance in a different way from aerobic exercise, with acute and repeated elevations in arterial blood pressure being associated with decreased arterial compliance (Miyachi *et al.* 2003, 2004; Kawano *et al.* 2008). Studies have hypothesized that increases in the smooth muscle tone and/or sympathetic nervous system activity, formation of collagen cross-linking or structural changes in the load-bearing properties of collagen and elastin occur to overcome high arterial pressures (Miyachi *et al.* 2004). Other studies of resistance training have shown no improvements in measures of arterial compliance (Rakobowchuk *et al.* 2005a; Poelkens *et al.* 2007) or arterial stiffness (Okamoto *et al.* 2006; Casey *et al.* 2007; Yoshizawa *et al.* 2009).

It is worth noting that the compliance of the veins may be responsive to exercise training. Monahan *et al.* (2001) reported that endurance-trained older men demonstrated 70–120% higher calf venous compliance than their inactive peers, and even young endurance-trained men demonstrated 30% greater venous compliance than sedentary young men. Hernandez & Franke (2005) showed 20–30% improvements in calf venous compliance with 6 months of endurance exercise training in older men and women. Such improvements in venous compliance may be related to the impact of the muscle pump during exercise. Changes in venous compliance may also be detrimental to orthostatic tolerance, although this putative link requires more empirical support (Hernandez & Franke, 2004, 2005).

In summary, aerobic exercise training improves local and central vascular compliance in subjects at known or increased risk of cardiovascular disease and in middle-aged and older sedentary subjects. In healthy young men there is little evidence that exercise training has a beneficial

effect on arterial compliance, perhaps because there is little impairment in arterial compliance *a priori*. The impact of exercise training on arterial compliance may also depend on the type of exercise performed. Some studies suggest that prolonged resistance training may be associated with decreases in arterial compliance.

Summary

It is now evident that direct measures of blood vessel function and structure provide independent prognostic indices of risk of cardiovascular disease in both symptomatic and asymptomatic individuals (Thijssen *et al.* 2010a). Strong evidence exists that decreases in cardiovascular risk associated with exercise training are associated with upregulation of endothelium-mediated vasodilator function and improvements in arterial compliance. Enhanced vessel function is observed in both trained and untrained limbs, suggesting that exercise has a beneficial systemic effect, which may relate to distinctive patterns of blood flow and shear stress. Such changes in shear and upregulation of the vasodilator pathways are also related to changes in arterial vasodilator capacity and wall-to-lumen ratios. The balance between training-induced changes in vasodilator function, arterial remodelling and vasoconstrictor tone requires further investigation, but current evidence suggests some compensatory increases in constriction may be apparent, at least at rest. Future work might focus on the most efficacious exercise prescriptions to bring about beneficial arterial adaptation and also investigate non-exercise models that might achieve the same outcomes in patients with significant pathology.

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