TOPICAL REVIEW

Physical (in)activity and endothelium-derived constricting factors: overlooked adaptations

D. H. J. Thijssen[1], G. A. Rongen[2], P. Smits[2] and M. T. E. Hopman[1]

Departments of [1] Physiology and [2] Pharmacology–Toxicology, Radboud University Nijmegen Medical Centre, the Netherlands

The inner surrounding of arterial vessels, the endothelium, is optimally located to detect changes in blood characteristics or blood flow that may result from changes in physical activity or from diseases. In response to physical stimuli, the endothelium varies its release of circulating vasoactive substances and serves as a source of local and systemic endothelium-derived dilator and vasoconstrictor factors. Endothelial dysfunction is one of the earliest markers of vascular abnormalities observed in cardiovascular disease and ageing. Exercise training is an efficient therapeutic strategy to improve endothelial function. Traditionally, studies on endothelial dysfunction and physical (in)activity-related effects on vascular adaptations are primarily focused on vasodilator substances (i.e. nitric oxide). One may suggest that augmentation of vasoconstrictor pathways (such as endothelin-1 and angiotensin II) contributes to the endothelial dysfunction observed after physical inactivity. Moreover, these pathways may also explain the exercise-induced beneficial cardiovascular adaptations. This review summarizes the current knowledge on the effects of physical (in)activity on several endothelium-derived vasoconstrictor substances.

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Corresponding author D. H. J. Thijssen: Radboud University Nijmegen Medical Centre, Department of Physiology, Geert Grooteplein-noord 21, 6525 EZ Nijmegen, the Netherlands. Email: d.thijssen@fysiol.umcn.nl

The importance of physical inactivity as a modifiable behavioural risk factor for cardiovascular disease is widely recognized (Wannamethee & Shaper, 2001). The endothelial function is suggested to underlie the physical activity-induced vascular adaptations. Situated between the circulating blood and the surrounding tissue, the endothelium is optimally located to detect changes in blood contents or blood flow that may result from physical (in)activity. In response, the endothelium varies its release of substances that modulate vascular tone (e.g. vasodilators and vasoconstrictors), structure (proliferative) or blood characteristics (e.g. coagulation pathway, inflammatory control).

Vasodilators in general, and nitric oxide (NO) specifically, have been the primary focus in explaining the mechanisms of vascular changes resulting from activity and inactivity. Several animal studies and human *in vivo* invasive studies (using pharmacological blockade or stimulation of vasodilators) have assessed the role of these vasodilators in the regulation of vascular tone. In an excellent recent review for this journal, Green *et al.* (2004) summarized these studies and described the importance of the endothelium-derived NO pathway for exercise-induced cardiovascular adaptations. Whilst the effects of the vasoactive substances on vascular tone and vascular growth largely depend on a delicate balance between dilators and constrictors (Spieker *et al.* 2006) (Fig. 1), there is a predominance of studies focusing on vasodilators (primarily NO) to explain exercise-induced adaptations. It may well be that exercise-induced changes are, at least in part, related to other pathways than NO. In addition, physical inactivity results in cardiovascular adaptations that are the opposite of the effects of exercise training. Given the effects of exercise training on the NO pathway, vascular changes to physical inactivity were hypothesized to result from an inhibition of the NO pathway. However, we (de Groot *et al.* 2004; Bleeker *et al.* 2005) and others (Bonnin *et al.* 2001) found a preserved contribution of NO to vascular tone and preserved NO-dependent endothelial function during inactivity.

The above results suggest that other pathways than solely vasodilator mechanisms may be involved in cardiovascular adaptation to changes in physical activity. In this review, we discuss findings regarding the contribution of endothelium-derived constricting factors in explaining cardiovascular adaptations during physical (in)activity in healthy subjects and in cardiovascular disease. Studies

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Table 1. Physical stimuli that stimulate or inhibit the pathways of endothelin-1 and angiotensin II

	Humoral stimuli		Physical/exogenous stimuli	
	Endothelin-1	Angiotensin II	Endothelin-1	Angiotensin II
Stimulators	Angiotensin	Endothelin	Pulsatile stretch	Pulsatile stretch
	Insulin	Insulin	Shear stress (low)	(cardiomyocytes)
	Cytokines	Cytokines	Osmolarity	Volume depletion
	Interleukin-1	Interleukin-1	Hypoxia	
	Oxidized LDL	Oxidized LDL		
	Vasopressin	Progesterone		
	Adrenalin			
	TGF-β			
	Endotoxin			
	Glucose			
Inhibitors	Nitric Oxide	Nitric oxide	Statins	Statins
	Oestrogens	Oestrogens	Shear stress (high)	Atrial distension
	Prostacyclin	FGF		
	Heparin	Free radicals		

LDL, low-density lipoprotein; FGF, fibroblast growth factor.

discussed in this review article related to (changes in) physical activity pertain to dynamic exercise rather than resistance exercise.

Endothelium-derived vasoconstricting factors

Endothelin-1. Endothelin-1 (ET-1) is the predominant isoform of the endothelin family and is mainly secreted by the endothelium (Yanagisawa *et al.* 1988) in response to a variety of stimuli (Table 1). The release of ET-1 results in activation of two receptors: ET_A and ET_B. Activation of the ET_A and ET_B receptors on the smooth muscle cell mediates a sustained constrictor action of ET-1. The ET_B receptors on the endothelium mediate the release of the dilators NO and prostacyclin, but also mediate the rapid uptake of ET-1 (Haynes & Webb, 1998). Therefore, the endothelial ET_B receptor largely opposes the vascular effect of smooth muscle cell-located $ET_{A/B}$ receptors. In addition to the direct vascular effects, ET-1 induces vascular smooth muscle cell proliferation and growth in a dose-dependent manner (Komuro *et al.* 1988).

Angiotensin II. After cleavage of angiotensinogen to angiotensin (Ang) I via renin, this peptide is cleaved by the angiotensin converting enzyme (produced by pulmonary and systemic vascular endothelium) into Ang II, which binds to its specific receptors on the vascular wall. Various stimuli alter the level of synthesis of Ang II (Table 1). Two well-described subtypes of the Ang II receptors, designated AT_1 and AT_2, have been identified. The smooth muscle cell-localized AT_1 receptor subtype mediates the predominant action of Ang II: vasoconstriction. These vasoactive actions are partly counteracted by the AT_2 receptor, which causes vasodilatation (Hernandez Schulman *et al.* 2007). Besides the vasoactive effects, Ang II leads to proliferation and growth of the vascular smooth muscle cells through activation of the AT_1 receptor.

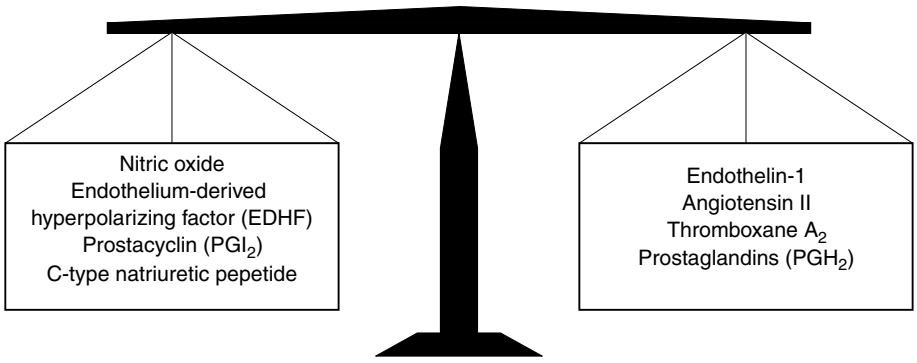

Figure 1. The delicate balance between endothelium-derived vasoactive substances contributing to the vascular tone

Thromboxane A_2. Thromboxane A_2 (TXA_2) is one of the end products of arachidonic acid metabolism and is produced by TXA_2 synthase. TXA_2 is primarily produced by platelets, but also by the endothelium. The physiological role of TXA_2 is platelet aggregation and vasoconstriction (Oates *et al.* 1988).

Prostaglandins. While prostaglandins have vasodilator effects, the prostaglandin H_2 (PGH_2) isoform is a vasoconstrictor substance. PGH_2 is closely related to TXA_2: both are formed during arachidonic acid metabolism, and PGH_2 is the precursor of TXA_2 and exerts its vascular effects through the same receptors on the vascular wall (Davidge, 2001).

We are not aware of any studies that have examined the potential role of TXA_2 or PGH_2 in cardiovascular changes during physical (in)activity. Therefore, the role of these two endothelium-derived vasoconstricting factors will not be discussed in this review.

Physical inactivity

Functional changes. While 5–18 days of space flight did not alter ET-1 plasma concentrations in humans (Meck *et al.* 2004), increased ET-1 plasma concentrations were observed after hindlimb unloading in rats (Biondi *et al.* 1995) and detraining in humans (Maeda *et al.* 2001). Short-term bed rest increased concentrations of Ang II (Haruna *et al.* 1997; Bestle *et al.* 2001). Paralysed muscles of spinal cord-injured individuals are subject to extreme inactivity and can therefore serve as a 'model of nature' for localized deconditioning. This population demonstrated high concentrations of ET-1 (Robergs *et al.* 1993), which increased even further after a period of training. Interpreting these scattered results, one should realize that plasma concentrations do not necessarily indicate a functional change in these pathways. In our lab, we examined ET-1 plasma concentrations *and* the ET-1-mediated leg vascular tone after intra-arterial blockade of $ET_{A/B}$ receptors using BQ-123 and BQ-788 in the same subjects (Thijssen *et al.* 2007*a*,*c*). Combining the results of these studies, we found that ET-1 plasma concentrations do not correlate with the contribution of ET to baseline vascular tone (Fig. 2). However, baseline leg blood flow and ET-1-mediated vascular tone showed an inverse relation ($r^2 = 0.12, P = 0.03$), indicating that a low leg blood flow correlates with an elevated ET-1-mediated vascular tone. This advocates the use of local infusion to assess the role of ET-1 to regulate vascular function, rather than plasma concentrations.

Recently, we examined the contribution of ET-1 to baseline blood flow in extremely inactive legs of spinal cord-injured (SCI) individuals, using an intrafemoral administration of selective $ET_{A/B}$ receptor blockers (Thijssen *et al.* 2007*a*). We demonstrated that ET-1 importantly contributes to the increased vascular tone observed during physical inactivity. This is supported by the reversed ET-1-mediated vascular tone in these subjects after 6 weeks of exercise training.

Regarding Ang II, it was demonstrated that significantly lower dosages are necessary in SCI individuals compared with able-bodied controls to achieve a similar increase in blood pressure (Krum *et al.* 1992). This suggests the presence of an exaggerated pressor response to Ang II in SCI individuals.

Structural changes. To date, no studies have examined the role of endothelium-derived vasoconstricting factors in the regulation of physical inactivity-induced structural changes, such as an inward remodelling of conduit arteries during inactivity.

Physcial activity as an intervention

Functional changes. Using a cross-sectional design, it was demonstrated that the ET-1-sensitivity, *ex vivo* examined using the concentration of ET-1 necessary to cause a 50% response (EC_{50}), of the aorta and coronary artery is reduced after a period of exercise training in swine (Jones *et al.* 1999). In addition, aortic and cerebellar arteries in exercise-trained rats have a diminished sensitivity to the actions of ET-1 on lipid metabolism compared with sedentary rats (Latorre *et al.* 2002). Moreover, the postischaemic sensitivity to ET-1 in coronary arteries was significantly lower in endurance-trained rats than in sedentary rats (Symons *et al.* 2000). Regarding the Ang II pathway, an exercise-induced decrease in Ang II-induced pulmonary vasoconstriction was present in rats that trained for 6 weeks (Kashimura *et al.* 1995).

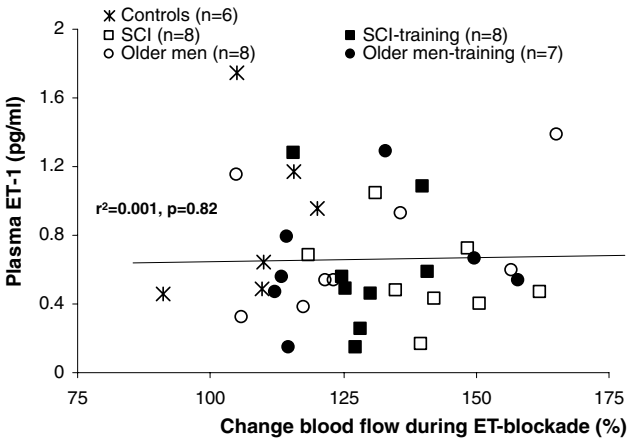

Figure 2. Correlation between the relative change in blood flow of the infused leg during ET blockade (representing the contribution of ET-1 to leg vascular tone) and baseline plasma concentrations of ET-1

In humans, only one single study examined potential differences in the regulation of vascular tone by Ang II between healthy athletic and sedentary men. A similar response is reported in forearm vascular bed for Ang II (but also for NO), between elite athletic and sedentary healthy men (Kingwell *et al.* 1996).

Structural changes. Based on their potent proliferative acivity, both ET-1 and Ang II contribute to pathological structural changes. This is supported by the inhibited formation of atherosclerotic lesions during prolonged ET_A receptor blockade (Barton *et al.* 1998) and by the accelerated atherosclerotic process during overexpression of the AT_1 receptor (Nickenig & Harrison, 2002). Regarding the effects of exercise, lower ET-1-mediated DNA expression in arteries was found in exercise trained swine compared with sedentary peers (Wamhoff *et al.* 2002). Because amounts of DNA synthesis are suggested to correlate with proliferative activity (and therefore atherosclerosis), decreased proliferative responses of constrictor pathways may contribute to the exercise-induced cardioprotection. In addition, ET-1 and Ang II are hypothesized to contribute to angiogenesis. Under hypoxic conditions, ET-1 induces angiogenesis via activation of the ET_B receptors (Goligorsky *et al.* 1999) and via enhanced expression of NO synthase (Liu *et al.* 2003), while Ang II results in angiogenesis through the actions of the vascular endothelial growth factor (Amaral *et al.* 2001).

Physical activity in specific groups

Ageing. Animal studies demonstrated that ET-1 (possibly through ET_A receptors) and Ang II (possibly through AT_2 receptors) contribute to the age-related increase in vascular tone in coronary arteries (Goodwin *et al.* 1999; Korzick *et al.* 2005), mesenteric vessels (Pinaud *et al.* 2007), gastrocnemius vascular bed (Donato *et al.* 2005), total vascular bed (Asai *et al.* 2001), and renal arteries (Tank *et al.* 1994). Recently, the pivotal role of ET-1 in the age-related increase in vascular tone was confirmed with human *in vivo* experiments in the lower (Thijssen *et al.* 2007*c*) as well as in the upper extremities (Van Guilder *et al.* 2007). In the forearm, this was possibly regulated via ET_A receptors (Van Guilder *et al.* 2007). Examining the potential beneficial effects of exercise training in ageing, it was demonstrated that 12 weeks of exercise in old rats did not change $ET_{A/B}$ receptor-mediated responsiveness, examined *ex vivo* using the EC_{50} value, of muscle arterioles (Donato *et al.* 2005). This finding is in contrast with two recent human *in vivo* studies, which reported a partly reversed ET-1-mediated vascular tone after exercise training in older men in the leg (Thijssen *et al.* 2007*c*) and forearm (Van Guilder *et al.* 2007) vascular bed. Based on these recent findings, it is hypothesized that the negative effects of ET-1 in cardiovascular disease, predominantly occurring in the ageing population, may be due to inactivity rather than to senesence (Thijssen *et al.* 2007*b*).

Coronary artery disease. It has been demonstrated that exercise training in patients with stable coronary artery disease leads to a 49% reduction in Ang II-induced vasoconstriction. Moreover, this adaptation is accompanied by lower expression of the AT_1 receptor and increased expression of the AT_2 receptor (Adams *et al.* 2005).

Pulmonary hypertension. Only one study so far has examined the vascular effects after 5 weeks of exercise training in pulmonary hypertensive rats on the ET pathway. While the pulmonary vasomotor function improved, the pulmonary vasoreactivity to vasoactive agents (e.g. ET-1) did not change (Goret *et al.* 2005). Pulmonary hypertension is the only widely accepted cardiovascular pathology that is treated with ET receptor blockers, so a large potential exists for exercise training to attenuate the central and peripheral vasoactive effects of the ET pathway in this disease.

Heart failure. Decreased plasma concentrations of Ang II have been reported after exercise training in rabbits with heart failure (Liu *et al.* 2000), while the significant up-regulation in AT_1 receptor mRNA in heart failure in rats is normalized after exercise training (Zucker *et al.* 2004). Also in patients with heart failure, improving physical fitness results in suppressing circulating concentrations of Ang II (Braith *et al.* 1999) and lowering of plasma concentrations of ET-1 (Kubanek *et al.* 2006).

Conclusions

The studies discussed in the present review suggest that inhibition of endothelium-derived vasoconstricing pathways contribute to exercise-induced vascular changes. Accordingly, cardiovascular adaptations to a change in physical activity are likely to be regulated through tight interactions between vasodilator (e.g. NO) and vasoconstrictor pathways (e.g. ET-1, Ang II). This may even be of special interest in disease states characterized by altered endothelium-derived constrictor pathways. Better insight into the underlying mechanisms (e.g. the role of the receptors and of the post receptor signalling pathways) will help us to understand the vascular changes observed in physical (in)activity. In addition, little is known regarding the role of endothelium-derived vasoconstictors in structural changes after exercise or inactivity. Also the field of vasoconstrictor prostanoids (TXA_2 and PGH_2) is relatively unexplored.

With respect to cardiovascular diseases, several scientific lines of evidence are present that support a central role for endothelium-derived vasoconstricting factors. Based on the summarized findings in this review, one should realize that the negative effects of ET-1 and Ang II in cardiovascular disease may be importantly confounded by the degree of inactivity. Therefore, inactivity, rather than the pathology of these specific cardiovascular diseases, is emerging as a strong candidate to explain the increased vascular tone. However, only a few studies examined the effect of exercise training on the role of these vasoconstricting factors. The sparse data at present suggest that exercise training potentially improves cardiovascular function in these patients (at least partly) through inhibition of the constrictor pathways. We strongly advocate that future studies should examine the potential for exercise training as a non-pharmacological intervention in cardiovascular diseases, and take particular interest in vasoconstrictor-related mechanisms to explain the possible beneficial cardiovascular effect.

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