

■ R E V I E W

Impact of exercise training on arterial wall thickness in humans

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A B S T R A C T

Thickening of the carotid artery wall has been adopted as a surrogate marker of pre-clinical atherosclerosis, which is strongly related to increased cardiovascular risk. The cardioprotective effects of exercise training, including direct effects on vascular function and lumen dimension, have been consistently reported in asymptomatic subjects and those with cardiovascular risk factors and diseases. In the present review, we summarize evidence pertaining to the impact of exercise and physical activity on arterial wall remodelling of the carotid artery and peripheral arteries in the upper and lower limbs. We consider the potential role of exercise intensity, duration and modality in the context of putative mechanisms involved in wall remodelling, including haemodynamic forces. Finally, we discuss the impact of exercise training in terms of primary prevention of wall thickening in healthy subjects and remodelling of arteries in subjects with existing cardiovascular disease and risk factors.

INTRODUCTION

Coronary and cerebrovascular diseases are leading causes of morbidity and mortality [1]. Exercise is associated with decreased cardiovascular risk [2,3] and higher fitness confers cardioprotection [4]. The beneficial effects of exercise on traditional risk factors may explain approximately half of the risk reduction associated with exercise [5,6], and it has been proposed that direct effects of exercise on the vessel wall may account for some of the remaining ‘risk factor gap’ [7,8]. One manifestation of exercise-mediated arterial adaptation is the change in carotid and peripheral wall thickness, which has not previously been reviewed. The purpose of the present review is therefore to describe the effect of exercise training on remodelling of the arterial wall in conduit arteries in healthy asymptomatic subjects and in those with cardiovascular risk factors or disease.

WHY IS THICKENING OF THE ARTERY WALL IMPORTANT?

Atherosclerosis can begin in early life [9], with impairment of endothelial function a likely precipitating event [10], followed by gradual remodelling of the arterial wall [11]. Although the process of atherothrombosis is dynamic, plaque evolution is prolonged and occult. These considerations emphasize the potential utility of tools which assess pre-clinical atherosclerotic changes *in vivo*. High-resolution ultrasound is able to detect arterial wall thickness and contemporary edge-detection algorithms can accurately measure IMT (intima-media thickness), which is a validated surrogate marker for atherosclerosis [12].

Clinical relevance of carotid artery wall thickness

Large follow-up trials, such as the ARIC (Atherosclerosis Risk in Communities) study [13,14] and the Rotterdam

Key words: cardiovascular disease, exercise training, intima-media thickness, physical fitness, vascular remodelling.

Abbreviations: ET-1, endothelin-1; FRS, Framingham Risk Score; ICAM-1, intercellular adhesion molecule-1; IMT, intima-media thickness; NOS, nitric oxide synthase; eNOS, endothelial NOS; PA, physical activity; ROS, reactive oxygen species; SNS, sympathetic nervous system; T1D, Type 1 diabetes; T2D, Type 2 diabetes; VCAM-1, vascular cell-adhesion molecule-1.

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study [15–17], have established that carotid IMT is associated with increased risk for adverse cerebral events (e.g. stroke), which is independent of other risk factors [13,15,17]. Carotid IMT may possess superior predictive capacity for stroke than other measures of atherosclerotic risk, such as the presence of carotid plaques and the ankle–arm index [16].

Increased carotid IMT is also associated with increased risk for cardiac (e.g. angina pectoris and myocardial infarction) [13,15,18–20] and peripheral vascular events (e.g. peripheral artery disease and hypertension) [21,22]. The annual change in carotid artery IMT represents a surrogate marker for systemic atherosclerosis and provides prognostic information [11]. A meta-analysis found that a 0.1 mm increase in carotid artery IMT is associated with an increase in age- and sex-adjusted relative risk of 18% for stroke and 15% for myocardial infarction [23]. A recent study confirmed the independent predictive capacity of carotid IMT in asymptomatic subjects and indicated that carotid IMT provided similar risk stratification as the FRS (Framingham Risk Score) [24].

Clinical relevance of wall thickness in peripheral arteries

Arteries of the lower limbs are subject to the development of atherosclerosis, plaque formation and clinical complications (e.g. intermittent claudication). Indeed, thickening of the arterial wall in older subjects is even found in arteries of the upper limbs, such as the brachial artery [25,26], in which plaque formation/rupture is not typically observed. The presence of arterial wall thickening in atherosclerosis-prone and -resistant vessels supports the idea that wall thickening occurs systemically [27]. Whether an age-related increase in wall thickness in these vessels reflects systemic atherosclerotic remodelling or benign age-related thickening of the wall (in some or all vessels) is currently unknown.

Studies have also established the clinical and prognostic value of peripheral artery wall thickness measures. For example, increased femoral artery IMT strongly relates to traditional cardiovascular risk factors, such as blood pressure, waist circumference, cholesterol, insulin and smoking status [28–30]. Thickening of the femoral wall also correlates with measures of peripheral atherosclerotic disease, such as the ankle–brachial index [31], and a significant relationship is present between femoral IMT and the FRS [29,32]. This strong association with cardiovascular risk factors suggests that femoral IMT may possess prognostic relevance. Studies have found associations between femoral IMT and restenosis after percutaneous coronary intervention [33] and with the severity and extent of coronary artery disease [34].

Advanced age is associated with the thickening of atherosclerosis-resistant arteries, such as the brachial artery [25,26]. A correlation exists between brachial and

carotid IMT [35], and the extent of atherosclerosis is also correlated between the brachial, carotid and coronary arteries [36]. These studies suggest that upper limb arterial wall thickening may be clinically and prognostically relevant. In a large population-based study, brachial artery IMT related strongly to the FRS in older subjects, with lipid levels [i.e. HDL (high-density lipoprotein); inversely] and oxidative stress [i.e. oxLDL (oxidized low-density lipoprotein); positively] related to brachial IMT [37]. Increased brachial IMT also correlates, independent of other cardiovascular risk factors, with the presence of coronary artery disease [38,39]. Previous studies also found that increased brachial IMT predicts future cardiovascular events in subjects undergoing coronary angiography [40] and that brachial IMT progression is linked with worsening disease severity in patients with heart failure [41]. Collectively, these findings suggest that brachial IMT is related to cardiovascular risk and may have a prognostic role in the prediction of cardiovascular events.

DOES EXERCISE TRAINING MODIFY CONDUIT ARTERIAL WALL THICKNESS?

PA (physical activity) and carotid arterial wall thickness

Studies which have examined the relationship between carotid IMT and daily PA levels have typically adopted a cross-sectional design and used questionnaires to assess PA (Table 1). When combined, studies including a total of >28 000 subjects found an inverse relationship between self-reported PA and carotid IMT [42–47]. This association is supported by the finding that higher *a priori* PA levels are related to attenuated 3- or 6-year increases in carotid IMT [42,47]. It must be noted that self-reported PA represents a subjective measure and correlates only modestly with direct measures of physical fitness [48]. Owing to these limitations, questionnaires may only provide meaningful data in large cohorts and with specifically designed instruments to assess PA. Yamada et al. [49], in a small sample ($n = 149$), found no relationship between IMT and PA level assessed using a non-specific questionnaire.

The limitations of PA measurement may explain inconsistent findings regarding the inverse correlation between PA levels and carotid IMT. For example, the association between higher leisure-time PA levels and lower carotid IMT in one analysis was present in never-smokers, but not smokers [45]. Data derived from the Tromso Study, a large population-based trial, identified sex and age as modulators of the inverse relationship between PA and carotid atherosclerosis [43,44]. More specifically, the inverse relationship between PA and carotid artery atherosclerosis was observed in men, but not women [43,44]. These researchers also found that the

Table 1 Cross-sectional studies investigating the impact of PA/physical fitness on arterial wall thickness in healthy volunteers

The 'Effect' indicates that a higher PA/physical fitness is related to a lower arterial IMT (+) or no difference in arterial IMT (~). Exercise history relates to the comparison between the groups that differ in training history. CA, carotid artery; FA, femoral artery; BA, brachial artery.

First author	<i>n</i>	Age (years)	Fitness measure	Artery	Effect
Hagg [50]	29	20–40	Exercise test	CA	+
Rauramaa [51]	163	50–60	Exercise test	CA	+
Sandrock [52]	101	64 ± 5	Exercise test	CA	+
Lee [53]	9871	40–81	Exercise test	CA	+
Lakka [57]	854	42–60	Exercise test	CA	+
Moreau [67]	173	20–79	Exercise history	FA	+
Rowley [61]	29	22 ± 3	Exercise history	CA-BA-FA	+
Moreau [60]	77	48–80	Exercise history	CA-FA	+(FA), ~(CA)
Tanaka [58]	137	18–77	Exercise history	CA	~
Popovic [59]	150	20–40	Exercise history	CA	~
Hamer [54]	530	63 ± 6	Walking speed	CA	+
Elbaz [55]	2572	65–85	Walking speed	CA	+
Bertoni [56]	6482	45–84	Walking speed	CA	+
Juonala [42]	1809	24–39	Questionnaire	CA	+
Stensland-Bugge [43]	6408	25–84	Questionnaire	CA	+(men + higher age)
Stensland-Bugge [44]	3128	25–84	Questionnaire	CA	+(men)
Luedemann [45]	1632	45–70	Questionnaire	CA	+(but not in smokers)
Folsom [46]	14 430	45–64	Questionnaire	CA	+
Nordstrom [47]	500	40–60	Questionnaire	CA	+(dose-dependent)
Yamada [49]	149	54 ± 12	Questionnaire	CA-FA	~
Kozakava [87]	495	44 ± 8	Accelerometry	CA	+
Kozakava [88]	432	43 ± 8	Accelerometry	CA	~

protective effects of a higher PA were more pronounced in older cohorts (i.e. 60–69 and >70 years) [43].

In summary, although measures of self-reported PA should be interpreted with caution, these studies indicate an inverse relationship between PA levels and carotid IMT. Moreover, limited cross-sectional evidence suggests that the effects of PA on carotid IMT may be more prominent in older subjects and in men.

Physical fitness and carotid arterial wall thickness

The 'gold-standard' measure of cardiorespiratory fitness in humans involves direct assessment of peak or maximal oxygen consumption in response to an exercise test (Table 1). Cross-sectional studies, predominantly performed in middle-aged and older humans, have reported that low fitness correlates independently with increased carotid IMT [50–52] and the presence of carotid plaque [53]. Studies which have used surrogate measures of fitness in relatively large cohorts have observed that higher walking speeds correlate with a lower carotid IMT [54–56]. Although measurement of fitness and IMT at a single time point does not provide information about progression, Lakka et al. [57] examined the 4-year change in carotid IMT and found that lower fitness in middle-

aged men was the strongest independent predictor of a 4-year increase in carotid IMT [57].

Effect of exercise training on carotid arterial wall thickness

One of the first studies to examine the effect of exercise training on atherosclerosis examined carotid artery IMT in 137 endurance-trained and sedentary men and found no significant difference between the groups [58]. Subsequent studies performed in younger [59] or older [60] cohorts also observed no difference in carotid atherosclerosis between endurance-trained subjects and sedentary controls. A recent study [61], however, found a significantly lower carotid artery IMT in elite squash players compared with less active controls. The difference in training intensity and/or load may explain these disparate results, as elite squash players exercised >22 h/week at high intensity [61], whereas others classified endurance training when exercising >3 h/week [59] or >5 days/week [58,60].

Longitudinal studies involving exercise training have directly examined the effect of 8–12 weeks of aerobic exercise in middle-aged [58] and older [62] subjects, but found no evidence that exercise training altered carotid artery IMT. Similarly, 8-week resistance training in young

Table 2 Studies directly examining the impact of exercise training on arterial wall thickness in healthy volunteers

The effect of the intervention relates to a decrease (+), increase (-) or no change (~) on IMT. Lifestyle modification, diet + exercise. CA, carotid artery; FA, femoral artery; BA, brachial artery.

First author	<i>n</i>	Age (years)	Type of training	Weeks	Artery	Effect of training on IMT
Tanaka [58]	18	52 ± 4	Aerobic exercise	12	CA	~
Dinenno [66]	22	51 ± 4	Aerobic exercise	12	FA	+
Thijssen [62]	8	70 ± 3	Aerobic exercise	8	CA + FA	~
Green [26]	16	59 ± 1	Aerobic exercise	24	BA + PA	+
Rauramaa [64]	140	57 ± 1	Aerobic exercise	312	CA	+ (in men not taking statins)
Okamoto [89]	20	19 ± 1	Resistance training	8	CA	~
Wildman [65]	353	44–50	Lifestyle modification	204	CA	+ (in post-menopausal women)
Thijssen [69]	11	22 ± 2	Handgrip exercise	8	BA	+

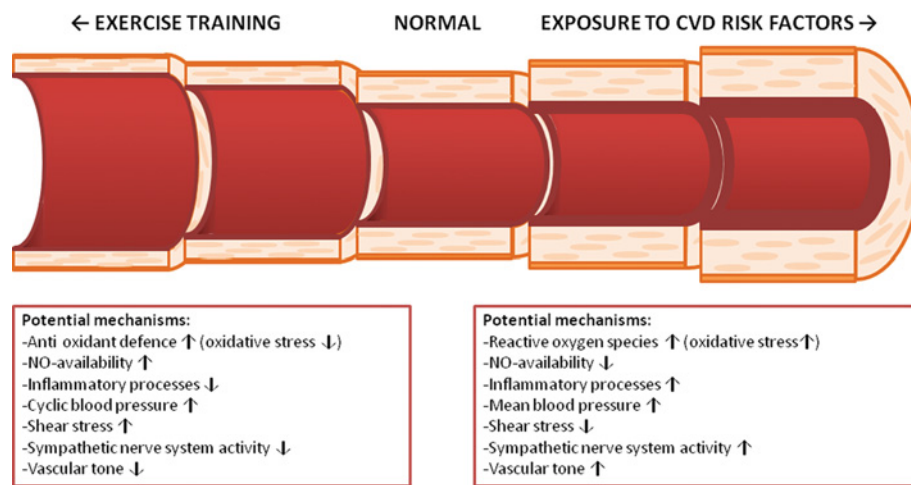


Figure 1 Impact of (prolonged and repetitive) exposure to cardiovascular risk factors (right-hand panel) and exercise training (left-hand panel)

Note the arterial wall thickening without changes in diameter associated with cardiovascular disease (CVD) risk factors, whereas exercise training is related to an outward remodelling of the arterial lumen and a decrease in wall thickness. The lower panels provides an overview of the potential mechanisms that may contribute to the changes in the arterial wall. Note that little evidence is currently available to support the mechanisms that contribute to the changes in arterial wall thickness during exercise training.

men did not alter carotid artery wall thickness [63]. In another study, Rauramaa et al. [64] examined the 6-year change in carotid IMT in 140 middle-aged men who performed aerobic exercise training or no intervention. They found no effect of exercise training, but a ~40% lower 6-year progression of carotid IMT when participants on statins ($n = 15$) were excluded, suggesting that the anti-atherosclerotic effects of statins may mask the impact of exercise. Another study examined the effect of a 4-year lifestyle intervention (PA + diet) in middle-aged women and found attenuated progression of carotid atherosclerosis in peri- and post-menopausal women, but not pre-menopausal women [65] (Table 2).

In summary, exercise training appears to have a modest effect on carotid artery atherosclerosis in young subjects (Figure 1) and changes may require intense exercise or interventions performed over prolonged time periods.

Effect of exercise training on wall thickness in peripheral arteries

A limited number of cross-sectional studies have examined the effect of exercise training on the wall thickness of peripheral arteries. In contrast with findings in the carotid artery, lower femoral artery IMT was observed in endurance-trained men and women compared with their sedentary peers [66,67]. Moreau et al. [60] extended this observation by comparing femoral and carotid artery IMT between endurance-trained athletes and sedentary controls. Although they confirmed the lower femoral artery IMT in athletes, no significant differences were observed between groups for carotid IMT. These findings suggest that exercise training may have a larger effect on remodelling of the arterial wall in peripheral arteries (that supply the active regions) than in the carotid arteries. Recently, Rowley et al. [61]

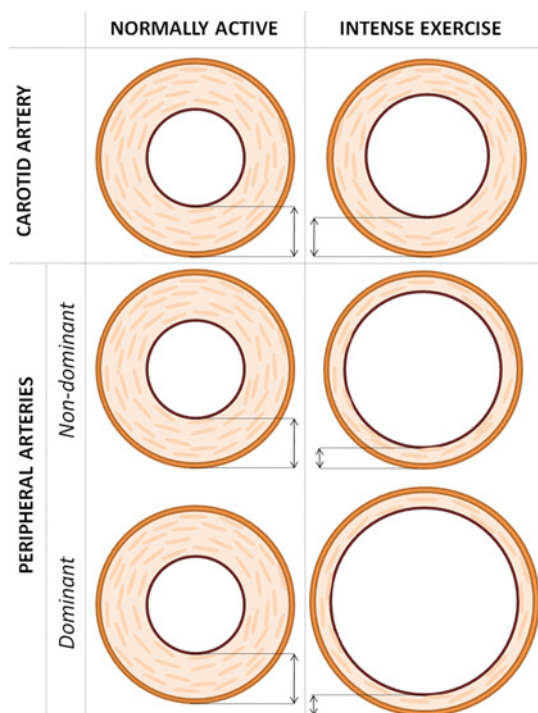


Figure 2 Brachial and carotid artery diameter and wall thickness in healthy recreationally active controls and elite squash players

Note the similar diameter and wall thickness between the dominant and non-dominant arm in controls, whereas squash players demonstrated a larger diameter in the dominant arm and smaller wall thickness in both arms. In addition, effects of exercise on arterial wall thickness seem to be more pronounced in peripheral arteries than the carotid artery. The Figure provides a summary of the results described in [61].

provided further support for this proposal (Figure 2) when they reported that elite squash players demonstrate a lower femoral, brachial and carotid artery IMT than sedentary controls. These findings support the presence of a generalized lower arterial wall thickness in highly trained athletes, than in controls.

Longitudinal training studies have also assessed changes in peripheral arterial wall thickness. Dinunno et al. [66] directly examined the impact of a 3-month aerobic exercise training programme on femoral artery IMT in middle-aged men and found a significant reduction in wall thickness. In addition, in older subjects, a decrease in peripheral arterial wall thickness (i.e. popliteal and brachial artery) was found after a 6-month aerobic exercise training [26], whereas no changes were observed after 8 weeks of training [62]. In a recent study, it was demonstrated that the increase in femoral IMT during 8 weeks of bed rest in young men can be (partly) prevented by (resistive) vibration exercise training [68]. Finally, a recent handgrip exercise training study found that localized exercise training can lead to

a small, but significant, decrease in brachial artery wall thickness [69]. Taken together, exercise training studies performed in healthy subjects indicate that remodelling occurs in response to prolonged training interventions in peripheral arteries supplying the active skeletal muscle.

EFFECT OF EXERCISE TRAINING ON WALL THICKNESS OF SUBJECTS WITH CARDIOVASCULAR DISEASE AND RISK FACTORS

Longitudinal exercise training studies of arterial wall thickness have predominantly been performed in obese subjects. Studies have reported beneficial effects of 26 [70,71] and 58 [72] weeks of aerobic exercise training on carotid IMT in obese children. In contrast, no change in carotid IMT was found in adults with obesity after 16–38 weeks of lifestyle modification [73] or 52 weeks of resistance training [74].

Jae et al. [75] examined cardiorespiratory fitness and carotid artery atherosclerosis (defined as a wall thickness >1.2 mm) in 2532 hypertensive men. After adjusting for established risk factors, an inverse relationship was observed between fitness and carotid atherosclerosis. Another study in 87 hypertensive subjects demonstrated that higher self-reported PA was associated with a lower 6.5-year increase in carotid IMT [76]. However, these beneficial effects could not be confirmed by Anderssen et al. [77], who found no effect of lifestyle modification on the 4-year progression in carotid IMT in hypertensive subjects.

An inverse relationship between self-reported PA level and carotid atherosclerosis has been described in patients with T2D (Type 2 diabetes) [78]. Another study found that lifestyle modification prevented the 0.5-year increase in carotid IMT in T2D [79]. In contrast, children with T1D (Type 1 diabetes) demonstrate no relationship between physical fitness and carotid IMT [80] and no change in carotid IMT after exercise training [81] (Table 3).

Finally, a prospective study involving hypercholesterolaemic men found that lifestyle modification (including a recommendation of exercise training) resulted in a regression of the 2-year increase in carotid IMT [82]. Another study examined the effect of aerobic and resistance exercise in heart failure patients on brachial artery IMT. Although aerobic exercise was not associated with a change in brachial artery wall thickness, resistance training significantly reduced brachial artery IMT [83].

Taken together, the studies described above suggest that exercise modifies arterial wall thickness in subjects with existing cardiovascular disease and risk factors. Further research is required to determine the degree of impact that exercise of different forms can have on sub-clinical atherosclerotic progression in humans.

Table 3 Studies investigating the impact of physical fitness on arterial wall thickness in subjects with cardiovascular disease/risk

The 'Effect' indicates that a higher PA/physical fitness is related to a lower arterial IMT (+) or no difference in arterial IMT (~). CA, carotid artery.

First author	Group	n	Age (years)	Fitness measure	Artery	Effect
Jae [75]	Hypertension	2532	52 ± 8	Exercise test	CA	+
Palatini [76]	Hypertension	87	31 ± 8	Questionnaire	CA	+
Trigona [80]	T1D	32	6–17	Exercise test	CA	~
Watarai [78]	T2D	53	53 ± 10	Questionnaire	CA	+

TIME COURSE OF ADAPTATIONS IN ARTERIAL WALL THICKNESS

Remodelling of the arterial wall is believed to occur over the time frame of months and years. In keeping with this, longitudinal studies of exercise training typically indicate that changes in arterial wall thickness occur across longer time periods (Tables 2 and 4). These observations are also consistent with the hypothesis that exercise training may initially induce functional arterial adaptation, which is followed by structural adaptations in the arterial wall with continued training [84,85]. Studies which have reported changes in arterial wall thickness as a result of brief interventions (8–12 weeks) [68,69,83] have examined peripheral arteries that supply the exercising region, such as the brachial (i.e. handgrip) and popliteal (i.e. cycling and running) arteries. This suggests that peripheral arteries exposed to a large stimulus for remodelling are capable of adapting more rapidly or that peripheral arteries feeding skeletal muscle possess enhanced intrinsic plasticity than arteries such as the carotids. Another possible explanation relates to changes in resting vascular tone. In a recent study [86], we found that administration of an NO donor resulted in immediate change in carotid and femoral artery IMT, raising the possibility that changes in conduit artery wall thickness in response to exercise training, especially those observed after a relatively short duration training, may relate in part to changes in vascular tone, rather than true structural wall remodelling.

DOES THE EXERCISE PRESCRIPTION HAVE AN IMPACT ON CHANGES IN WALL THICKNESS?

Nordstrom et al. [47] examined the 3-year change in carotid IMT and related this to different levels of leisure-time PA. They found a dose-dependent relationship between the self-reported PA level and the 3-year increase in carotid IMT. The presence of a dose-dependent relationship is supported by others, who have demonstrated with accelerometry that performance of vigorous leisure-time exercise [87], but not average daily PA levels [88], was related to an attenuated 3-year increase

in carotid IMT (Table 1). Higher exercise intensity may therefore relate to enhanced remodelling of the arterial wall.

Exercise modality may impact on the change in wall thickness. Most training studies have examined the effect of aerobic exercise on arterial wall thickness (Tables 2 and 4), with some studies also examining alternative training forms, such as resistance training [63,74,83,89]. However, a direct comparison between exercise modality is rare. Maiorana et al. [83] recently compared the effect of aerobic compared with resistance exercise in heart failure patients on the brachial artery IMT. Although aerobic exercise was not associated with a change in brachial artery wall thickness, resistance training significantly reduced IMT. This finding may be specific to patients with congestive heart failure, in whom resistance training may be particularly beneficial [90,91]. Future studies are warranted to identify the optimal exercise training regime to improve arterial wall thickness.

MECHANISMS RESPONSIBLE FOR CHANGES IN ARTERIAL WALL THICKNESS IN RESPONSE TO EXERCISE TRAINING

In some studies, the relationship between PA and IMT is independent of cardiovascular risk factors [53,57]. This suggests that the effect of exercise training on arterial wall thickness cannot be entirely explained by exercise-mediated changes in traditional cardiovascular risk factors, such as lipid levels, adiposity and blood pressure. This is supported by studies which have demonstrated the impact of exercise training on IMT in the absence of changes in risk factors [66,69,79,83] and others that reported an inverse correlation between carotid IMT and fitness, independent of risk factors [53,57]. We summarize some alternative pathways to explain the change in IMT after exercise training.

Role of local haemodynamic stimuli: shear stress

Shear stress plays an important role in the regulation of large artery remodelling [92], and the development of carotid atheromatous plaques has been linked with

Table 4 Studies directly examining the impact of exercise training on arterial wall thickness in subjects with cardiovascular disease/risk

The effect of the intervention relates to a decrease (+), increase (−) or no change (∼) on IMT. Lifestyle modification includes diet + exercise. CA, carotid artery; BA, brachial artery; CAD, coronary artery disease.

First author	Group	n	Age (years)	Type of training	Weeks	Artery	Effect
Olsen [74]	Obesity	30	24–44	Resistance training	52	CA	∼
Farpour-Lambert [70]	Obesity	22	9 ± 2	Aerobic training	26	CA	+
Woo [72]	Obesity	21	9–12	Aerobic training	58	CA	+
Skilton [73]	Obesity	39	44 ± 1	Lifestyle modification	16–38	CA	∼
Meyer [71]	Obesity	102	11–16	Aerobic exercise	26	CA	+
Maiorana [83]	Heart failure	12	61 ± 3	Aerobic exercise	12	BA	∼ (aerobic)
		12	59 ± 4	Resistance training	12	BA	+ (resistance)
Okada [82]	Hypercholesterolaemia	596	57 ± 12	Lifestyle modification	104	CA	+
Chan [113]	CAD	156	56 ± 6	Lifestyle modification	104	CA	∼
Kim [79]	T2D	58	54 ± 9	Lifestyle modification	26	CA	+
Seeger [81]	T1D	7	11 ± 2	Aerobic training	18	CA	∼
Anderssen [77]	Hypertension	568	40–74	Lifestyle modification	208	CA	∼

the presence of low mean shear rate [93]. Development of carotid plaques has also been related to oscillatory shear stress [93,94]. Such oscillatory shear patterns are characterized by shear that is not unidirectional, but rather goes in both directions, i.e. forward and backward. This observation is in agreement with studies performed *in vitro* [95] and *in vivo* [96], which reported a pro-atherogenic endothelial cell phenotype or function when these cells were exposed to increased levels of shear into the backward direction (i.e. retrograde shear stress). Specifically, oscillatory shear has been associated with decreased endothelial NOS (nitric oxide synthase) mRNA and increased VCAM-1 (vascular cell-adhesion molecule-1), ICAM-1 (intercellular adhesion molecule-1) and ET-1 (endothelin-1) [97,98]. Although exercise leads to an increase in shear in exercising and non-exercising regions [99,100], few studies have examined whether shear stress contributes to arterial wall remodelling.

Recently, we compared brachial artery wall thickness and diameter between the preferred and non-preferred limbs of elite squash players, with the assumption that the preferred limb of squash players receives a larger shear stress stimulus than the non-preferred limb over a prolonged period [61]. This model allows the isolation of localized effects on arterial function and structure, given that central haemodynamics and sympathetic nervous system tone are controlled for using bilateral limb comparisons. Interestingly, wall thickness did not differ between the preferred and non-preferred limbs, despite a larger arterial diameter on the preferred side (Figure 2). In another study, we directly examined the role of shear stress by performing bilateral handgrip exercise training, while unilaterally manipulating shear stress using cuff inflation during repeated exercise bouts [69]. Although shear was kept near resting levels during handgrip exercise in one arm, exercise training induced a similar decrease

in brachial artery wall thickness bilaterally. These studies suggest that systemic, rather than localized, shear stress plays an important role in adaptations of the arterial wall in response to exercise training.

Role of systemic haemodynamic stimuli: arterial pressure

During the cardiac cycle, blood pressure rapidly fluctuates and produces stretch on the arterial wall. Data collected *in vitro* demonstrate that chronic increases in blood pressure result in pro-atherogenic endothelial cell phenotypes, which are characterized by lower eNOS (endothelial NOS) mRNA expression and higher levels of VCAM-1, ICAM-1, ET-1 and ROS (reactive oxygen species) [98]. These findings support the clinical observation that a chronic increase in blood pressure relates to a thicker carotid arterial wall [101]. Moreover, a previous study in humans found that chronic elevations in local distending pressure in the carotid artery importantly contribute to arterial wall thickening [102]. Interestingly, exercise increases arterial pressure and, consequently, leads to a larger stretch on the arterial wall during exercise. Nonetheless, chronic exercise training is associated with a lower arterial wall thickness (Tables 2 and 4). It can therefore be speculated that up-regulation of pro- (e.g. VCAM-1, ICAM-1, ET-1 and ROS) and anti-atherogenic (e.g. eNOS) genes differ when the pressure stimulus involves chronic elevation compared with the transient, episodic and cyclical increases in blood pressure which occur in response to exercise [97,98]. Although findings are conflicting and primarily relate to responses of individual cells (excluding the cross-talk between cells), some evidence indicates that short-term cyclic elevation in pressure induces anti-atherogenic changes in the arterial wall (for a review, see [97]). However, this is

speculative at present and research in this area is in its infancy. Future studies are needed to clarify the role of specific patterns of blood pressure as stimuli for arterial wall remodelling.

Role of systemic non-haemodynamic stimuli

Vascular tone

The carotid and femoral artery walls are directly influenced by changes in vascular tone, since any decreases in wall thickness are observed when vascular tone is acutely modified [86]. Previous studies have found that exercise training can alter peripheral vascular tone, possibly contributing to a decrease in arterial wall thickness.

SNS (sympathetic nervous system)

Results from animal studies indicate that a sustained elevation of SNS tone stimulates smooth muscle cell hypertrophy [103]. Interestingly, SNS activity and femoral artery IMT in healthy young and older men are strongly correlated [101]. This suggests that SNS activity levels may contribute to changes in arterial wall thickness. Although exercise training is associated with decreased levels of resting SNS activity in clinical groups [104], conflicting results are apparent in healthy individuals [105], with some evidence supporting higher resting SNS activity in endurance-trained middle-aged and older subjects [106,107]. It is currently unknown whether changes in SNS activity and IMT as a result of exercise training are correlated, and whether this potential relation differs between groups.

Oxidative stress

Elevated levels of oxidative stress, which represent a balance between the production of ROS and the efficiency of antioxidant defences, induce endothelial dysfunction and are believed to contribute to the development of atherosclerosis [108,109]. Exercise training, especially when performed at moderate-intensity levels, is associated with antioxidant effects [110]. Therefore exercise-training-associated improvement of antioxidant defences (e.g. superoxide dismutase) may lower oxidative stress in the arterial wall and consequently contribute to decreased arterial wall thickness. However, to date, no study has directly examined the potential link between oxidative stress and arterial remodelling as a result of exercise training and should be subject for future research.

Inflammation

The importance of inflammatory processes during the development of carotid atherosclerosis is commonly accepted [111]. Exercise training is associated with anti-inflammatory effects, which are believed to contribute to the cardioprotective effects of an active lifestyle [112]. On the basis of these observational findings, it

is possible to speculate that exercise training may alter arterial wall thickness or plaque stability through an impact on inflammation. However, no direct evidence is currently available regarding this hypothesis. Future studies should examine the potential role of (anti-) inflammatory responses to contribute to the effect of exercise training on the arterial wall.

SUMMARY AND FUTURE DIRECTIONS

Exercise training can decrease arterial wall thickness in healthy asymptomatic subjects as well as in subjects with cardiovascular risk factors and/or disease that demonstrate increased arterial wall thickness *a priori*. However, differences exist between arteries, since exercise training has more pronounced effects on large peripheral arteries than the carotids. Modification of carotid wall thickness may require more intense or prolonged exercise exposure. Changes in arterial wall thickness may contribute to the cardioprotective effects of exercise, which are not fully explained by effects of traditional risk factors. However, many questions remain unanswered. Little is known regarding the duration, type and intensity of exercise training necessary to induce optimal benefits on the arterial wall and it is unclear whether these effects differ between healthy subjects and clinical groups. Moreover, the mechanisms that explain changes in the arterial wall as a result of exercise training are not fully understood. Identifying these stimuli will help in the design and recommendation of optimal exercise training protocols to attenuate atherosclerosis burden and risk. Technical advances and newer imaging technologies [e.g. MRI (magnetic resonance imaging) and strain echography] will assist in answering important questions regarding the impact of exercise training on arterial structure and remodelling in future.

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REFERENCES

- 1 World Health Organization (2008), The Global Burden of Disease: 2004 Update, World Health Organization, Geneva
- 2 Blair, S. N. and Morris, J. N. (2009) Healthy hearts: and the universal benefits of being physically active: physical activity and health. *Ann. Epidemiol.* **19**, 253–256
- 3 Taylor, R. S., Brown, A., Ebrahim, S., Jolliffe, J., Noorani, H., Rees, K., Skidmore, B., Stone, J. A., Thompson, D. R. and Oldridge, N. (2004) Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. *Am. J. Med.* **116**, 682–692

- 4 Kodama, S., Saito, K., Tanaka, S., Maki, M., Yachi, Y., Asumi, M., Sugawara, A., Totsuka, K., Shimano, H., Ohashi, Y. et al. (2009) Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA, J. Am. Med. Assoc.* **301**, 2024–2035
- 5 Maiorana, A., O'Driscoll, G., Taylor, R. and Green, D. (2003) Exercise and the nitric oxide vasodilator system. *Sports Med.* **33**, 1013–1035
- 6 Mora, S., Cook, N., Buring, J. E., Ridker, P. M. and Lee, I. M. (2007) Physical activity and reduced risk of cardiovascular events: potential mediating mechanisms. *Circulation* **116**, 2110–2118
- 7 Joyner, M. J. and Green, D. J. (2009) Exercise protects the cardiovascular system: effects beyond traditional risk factors. *J. Physiol.* **587**, 5551–5558
- 8 Green, D. J., O'Driscoll, G., Joyner, M. J. and Cable, N. T. (2008) Exercise and cardiovascular risk reduction: time to update the rationale for exercise? *J. Appl. Physiol.* **105**, 766–768
- 9 Tuzcu, E. M., Kapadia, S. R., Tutar, E., Ziada, K. M., Hobbs, R. E., McCarthy, P. M., Young, J. B. and Nissen, S. E. (2001) High prevalence of coronary atherosclerosis in asymptomatic teenagers and young adults: evidence from intravascular ultrasound. *Circulation* **103**, 2705–2710
- 10 Celermajer, D. S., Sorensen, K. E., Gooch, V. M., Spiegelhalter, D. J., Miller, O. I., Sullivan, I. D., Lloyd, J. K. and Deanfield, J. E. (1992) Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet* **340**, 1111–1115
- 11 de Groot, E., van Leuven, S. I., Duivenvoorden, R., Meuwese, M. C., Akdim, F., Bots, M. L. and Kastelein, J. J. (2008) Measurement of carotid intima-media thickness to assess progression and regression of atherosclerosis. *Nat. Clin. Pract. Cardiovasc. Med.* **5**, 280–288
- 12 de Groot, E., Hovingh, G. K., Wiegman, A., Duriez, P., Smit, A. J., Fruchart, J. C. and Kastelein, J. J. (2004) Measurement of arterial wall thickness as a surrogate marker for atherosclerosis. *Circulation* **109**, III33–III38
- 13 Chambless, L. E., Shahar, E., Sharrett, A. R., Heiss, G., Wijnberg, L., Paton, C. C., Sorlie, P. and Toole, J. F. (1996) Association of transient ischemic attack/stroke symptoms assessed by standardized questionnaire and algorithm with cerebrovascular risk factors and carotid artery wall thickness. The ARIC Study, 1987–1989. *Am. J. Epidemiol.* **144**, 857–866
- 14 Heiss, G., Sharrett, A. R., Barnes, R., Chambless, L. E., Szklo, M. and Alzola, C. (1991) Carotid atherosclerosis measured by B-mode ultrasound in populations: associations with cardiovascular risk factors in the ARIC study. *Am. J. Epidemiol.* **134**, 250–256
- 15 Bots, M. L., Hoes, A. W., Koudstaal, P. J., Hofman, A. and Grobbee, D. E. (1997) Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. *Circulation* **96**, 1432–1437
- 16 Hollander, M., Hak, A. E., Koudstaal, P. J., Bots, M. L., Grobbee, D. E., Hofman, A., Witteman, J. C. and Breteler, M. M. (2003) Comparison between measures of atherosclerosis and risk of stroke: the Rotterdam Study. *Stroke* **34**, 2367–2372
- 17 Hollander, M., Bots, M. L., Del Sol, A. I., Koudstaal, P. J., Witteman, J. C., Grobbee, D. E., Hofman, A. and Breteler, M. M. (2002) Carotid plaques increase the risk of stroke and subtypes of cerebral infarction in asymptomatic elderly: the Rotterdam Study. *Circulation* **105**, 2872–2877
- 18 Ebrahim, S., Papacosta, O., Whincup, P., Wannamethee, G., Walker, M., Nicolaides, A. N., Dhanjil, S., Griffin, M., Belcaro, G., Rumley, A. and Lowe, G. D. (1999) Carotid plaque, intima media thickness, cardiovascular risk factors, and prevalent cardiovascular disease in men and women: the British Regional Heart Study. *Stroke* **30**, 841–850
- 19 O'Leary, D. H., Polak, J. F., Kronmal, R. A., Manolio, T. A., Burke, G. L. and Wolfson, Jr, S. K. (1999) Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N. Engl. J. Med.* **340**, 14–22
- 20 Johnsen, S. H., Mathiesen, E. B., Joakimsen, O., Stensland, E., Wilsgaard, T., Lochen, M. L., Njolstad, I. and Arnesen, E. (2007) Carotid atherosclerosis is a stronger predictor of myocardial infarction in women than in men: a 6-year follow-up study of 6226 persons: the Tromso Study. *Stroke* **38**, 2873–2880
- 21 Wattanakit, K., Folsom, A. R., Selvin, E., Weatherley, B. D., Pankow, J. S., Brancati, F. L. and Hirsch, A. T. (2005) Risk factors for peripheral arterial disease incidence in persons with diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. *Atherosclerosis* **180**, 389–397
- 22 Chambless, L. E., Folsom, A. R., Davis, V., Sharrett, R., Heiss, G., Sorlie, P., Szklo, M., Howard, G. and Evans, G. W. (2002) Risk factors for progression of common carotid atherosclerosis: the Atherosclerosis Risk in Communities Study, 1987–1998. *Am. J. Epidemiol.* **155**, 38–47
- 23 Lorenz, M. W., Markus, H. S., Bots, M. L., Rosvall, M. and Sitzer, M. (2007) Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation* **115**, 459–467
- 24 Lorenz, M. W., Schaefer, C., Steinmetz, H. and Sitzer, M. (2010) Is carotid intima media thickness useful for individual prediction of cardiovascular risk? Ten-year results from the Carotid Atherosclerosis Progression Study (CAPS). *Eur. Heart J.* **31**, 2041–2048
- 25 Bjarnegard, N. and Lanne, T. (2010) Arterial properties along the upper arm in humans: age-related effects and the consequence of anatomical location. *J. Appl. Physiol.* **108**, 34–38
- 26 Green, D. J., Swart, A., Exterkate, A., Naylor, L. H., Black, M. A., Cable, N. T. and Thijssen, D. H. (2010) Impact of age, sex and exercise on brachial and popliteal artery remodelling in humans. *Atherosclerosis* **210**, 525–530
- 27 Grobbee, D. E. and Bots, M. L. (1994) Carotid artery intima-media thickness as an indicator of generalized atherosclerosis. *J. Intern. Med.* **236**, 567–573
- 28 Paul, T. K., Srinivasan, S. R., Chen, W., Li, S., Bond, M. G., Tang, R. and Berenson, G. S. (2005) Impact of multiple cardiovascular risk factors on femoral artery intima-media thickness in asymptomatic young adults (the Bogalusa Heart Study). *Am. J. Cardiol.* **95**, 469–473
- 29 Paul, T. K., Chen, W., Srinivasan, S. R., Rice, J., Toprak, A., He, J. and Berenson, G. S. (2010) Framingham risk score is associated with femoral artery intima-media thickness in asymptomatic young adults (the Bogalusa heart study). *Atherosclerosis* **213**, 627–631
- 30 Joensuu, T., Salonen, R., Winblad, I., Korpela, H. and Salonen, J. T. (1994) Determinants of femoral and carotid artery atherosclerosis. *J. Intern. Med.* **236**, 79–84
- 31 Suurkula, M., Fagerberg, B., Wendelhag, I., Agewall, S. and Wikstrand, J. (1996) Atherosclerotic disease in the femoral artery in hypertensive patients at high cardiovascular risk. The value of ultrasonographic assessment of intima-media thickness and plaque occurrence. *Arterioscler. Thromb. Vasc. Biol.* **16**, 971–977
- 32 Rietzschel, E. R., De Buyzere, M. L., Duprez, D. A. and Clement, D. L. (2001) Interchangeability of carotid and femoral intima-media thickness in risk stratification. *Int. Angiol.* **20**, 38–46
- 33 Novo, G., Maniglia, D., Corrado, E., Muratori, I., Suter, F., Evola, S., Ferrara, F., Hoffmann, E. and Novo, S. (2007) Peripheral atherosclerosis is associated with the occurrence of restenosis after percutaneous coronary intervention. *Coron. Artery Dis.* **18**, 627–631
- 34 Lekakis, J. P., Papamichael, C. M., Cimponeriu, A. T., Stamatiopoulos, K. S., Papaioannou, T. G., Kanakakis, J., Alevizaki, M. K., Papapanagiotou, A., Kalofoutis, A. T. and Stamatiopoulos, S. F. (2000) Atherosclerotic changes of extracoronary arteries are associated with the extent of coronary atherosclerosis. *Am. J. Cardiol.* **85**, 949–952
- 35 Agewall, S., Henareh, L. and Jogestrand, T. (2005) Intima-media complex of both the brachial artery and the common carotid artery are associated with left ventricular hypertrophy in patients with previous myocardial infarction. *J. Hypertens.* **23**, 119–125

- 36 Sorensen, K. E., Kristensen, I. B. and Celermajer, D. S. (1997) Atherosclerosis in the human brachial artery. *J. Am. Coll. Cardiol.* **29**, 318–322
- 37 Lind, L., Andersson, J., Ronn, M., Gustavsson, T., Holdfelt, P., Hulthe, J., Elmgren, A., Zilmer, K. and Zilmer, M. (2008) Brachial artery intima-media thickness and echogenicity in relation to lipids and markers of oxidative stress in elderly subjects: the prospective investigation of the vasculature in Uppsala Seniors (PIVUS) Study. *Lipids* **43**, 133–141
- 38 Weidinger, F., Frick, M., Alber, H. F., Ulmer, H., Schwarzacher, S. P. and Pachinger, O. (2002) Association of wall thickness of the brachial artery measured with high-resolution ultrasound with risk factors and coronary artery disease. *Am. J. Cardiol.* **89**, 1025–1029
- 39 Frick, M., Schwarzacher, S. P., Alber, H. F., Rinner, A., Ulmer, H., Pachinger, O. and Weidinger, F. (2002) Morphologic rather than functional or mechanical sonographic parameters of the brachial artery are related to angiographically evident coronary atherosclerosis. *J. Am. Coll. Cardiol.* **40**, 1825–1830
- 40 Frick, M., Suessbacher, A., Alber, H. F., Dichtl, W., Ulmer, H., Pachinger, O. and Weidinger, F. (2005) Prognostic value of brachial artery endothelial function and wall thickness. *J. Am. Coll. Cardiol.* **46**, 1006–1010
- 41 Poelzl, G., Frick, M., Huegel, H., Lackner, B., Alber, H. F., Mair, J., Herold, M., Schwarzacher, S., Pachinger, O. and Weidinger, F. (2005) Chronic heart failure is associated with vascular remodeling of the brachial artery. *Eur. J. Heart Failure* **7**, 43–48
- 42 Juonala, M., Viikari, J. S., Kahonen, M., Taittonen, L., Laitinen, T., Hutri-Kahonen, N., Lehtimäki, T., Jula, A., Pietikainen, M., Jokinen, E. et al. (2010) Life-time risk factors and progression of carotid atherosclerosis in young adults: the Cardiovascular Risk in Young Finns study. *Eur. Heart J.* **31**, 1745–1751
- 43 Stensland-Bugge, E., Bonna, K. H. and Joakimsen, O. (2001) Age and sex differences in the relationship between inherited and lifestyle risk factors and subclinical carotid atherosclerosis: the Tromso study. *Atherosclerosis* **154**, 437–448
- 44 Stensland-Bugge, E., Bonna, K. H., Joakimsen, O. and Njolstad, I. (2000) Sex differences in the relationship of risk factors to subclinical carotid atherosclerosis measured 15 years later: the Tromso study. *Stroke* **31**, 574–581
- 45 Luedemann, J., Schminke, U., Berger, K., Piek, M., Willich, S. N., Doring, A., John, U. and Kessler, C. (2002) Association between behavior-dependent cardiovascular risk factors and asymptomatic carotid atherosclerosis in a general population. *Stroke* **33**, 2929–2935
- 46 Folsom, A. R., Eckfeldt, J. H., Weitzman, S., Ma, J., Chambless, L. E., Barnes, R. W., Cram, K. B. and Hutchinson, R. G. (1994) Relation of carotid artery wall thickness to diabetes mellitus, fasting glucose and insulin, body size and physical activity. *Stroke* **25**, 66–73
- 47 Nordstrom, C. K., Dwyer, K. M., Merz, C. N., Shircore, A. and Dwyer, J. H. (2003) Leisure time physical activity and early atherosclerosis: the Los Angeles Atherosclerosis Study. *Am. J. Med.* **115**, 19–25
- 48 Mikkelsen, L., Kaprio, J., Kautiainen, H., Kujala, U. M. and Nupponen, H. (2005) Associations between self-estimated and measured physical fitness among 40-year-old men and women. *Scand. J. Med. Sci. Sports* **15**, 329–335
- 49 Yamada, S., Inaba, M., Goto, H., Nagata-Sakurai, M., Kumeda, Y., Imanishi, Y., Emoto, M., Ishimura, E. and Nishizawa, Y. (2006) Associations between physical activity, peripheral atherosclerosis and bone status in healthy Japanese women. *Atherosclerosis* **188**, 196–202
- 50 Hagg, U., Wandt, B., Bergstrom, G., Volkman, R. and Gan, L. M. (2005) Physical exercise capacity is associated with coronary and peripheral vascular function in healthy young adults. *Am. J. Physiol. Heart Circ. Physiol.* **289**, H1627–H1634
- 51 Rauramaa, R., Rankinen, T., Tuomainen, P., Vaisanen, S. and Mercuri, M. (1995) Inverse relationship between cardiorespiratory fitness and carotid atherosclerosis. *Atherosclerosis* **112**, 213–221
- 52 Sandrock, M., Schulze, C., Schmitz, D., Dickhuth, H. H. and Schmidt-Trucksass, A. (2008) Physical activity throughout life reduces the atherosclerotic wall process in the carotid artery. *Br. J. Sports Med.* **42**, 839–844
- 53 Lee, C. D., Jae, S. Y., Iribarren, C., Pettee, K. K. and Choi, Y. H. (2009) Physical fitness and carotid atherosclerosis in men. *Int. J. Sports Med.* **30**, 672–676
- 54 Hamer, M., Kivimäki, M., Lahiri, A., Yerramasu, A., Deanfield, J. E., Marmot, M. G. and Steptoe, A. (2010) Walking speed and subclinical atherosclerosis in healthy older adults: the Whitehall II study. *Heart* **96**, 380–384
- 55 Elbaz, A., Ripert, M., Tavernier, B., Fevrier, B., Zureik, M., Garipey, J., Alperovitch, A. and Tzourio, C. (2005) Common carotid artery intima-media thickness, carotid plaques and walking speed. *Stroke* **36**, 2198–2202
- 56 Bertoni, A. G., Whitt-Glover, M. C., Chung, H., Le, K. Y., Barr, R. G., Mahesh, M., Jenny, N. S., Burke, G. L. and Jacobs, D. R. (2009) The association between physical activity and subclinical atherosclerosis: the Multi-Ethnic Study of Atherosclerosis. *Am. J. Epidemiol.* **169**, 444–454
- 57 Lakka, T. A., Laukkanen, J. A., Rauramaa, R., Salonen, R., Lakka, H. M., Kaplan, G. A. and Salonen, J. T. (2001) Cardiorespiratory fitness and the progression of carotid atherosclerosis in middle-aged men. *Ann. Intern. Med.* **134**, 12–20
- 58 Tanaka, H., Seals, D. R., Monahan, K. D., Clevenger, C. M., DeSouza, C. A. and Dinunno, F. A. (2002) Regular aerobic exercise and the age-related increase in carotid artery intima-media thickness in healthy men. *J. Appl. Physiol.* **92**, 1458–1464
- 59 Popovic, M., Puchner, S., Endler, G., Foraschik, C., Minar, E. and Bucek, R. A. (2010) The effects of endurance and recreational exercise on subclinical evidence of atherosclerosis in young adults. *Am. J. Med. Sci.* **339**, 332–336
- 60 Moreau, K. L., Donato, A. J., Seals, D. R., Dinunno, F. A., Blackett, S. D., Hoetzer, G. L., Desouza, C. A. and Tanaka, H. (2002) Arterial intima-media thickness: site-specific associations with HRT and habitual exercise. *Am. J. Physiol. Heart Circ. Physiol.* **283**, H1409–H1417
- 61 Rowley, N. J., Dawson, E. A., Birk, G. K., Cable, N. T., George, K., Whyte, G., Thijssen, D. H. and Green, D. J. (2011) Exercise and arterial adaptation in humans: uncoupling localized and systemic effects. *J. Appl. Physiol.* **110**, 1190–1195
- 62 Thijssen, D. H., de Groot, P. C., Smits, P. and Hopman, M. T. (2007) Vascular adaptations to 8-week cycling training in older men. *Acta Physiol.* **190**, 221–228
- 63 Rakobowchuk, M., McGowan, C. L., de Groot, P. C., Hartman, J. W., Phillips, S. M. and MacDonald, M. J. (2005) Endothelial function of young healthy males following whole body resistance training. *J. Appl. Physiol.* **98**, 2185–2190
- 64 Rauramaa, R., Halonen, P., Vaisanen, S. B., Lakka, T. A., Schmidt-Trucksass, A., Berg, A., Penttila, I. M., Rankinen, T. and Bouchard, C. (2004) Effects of aerobic physical exercise on inflammation and atherosclerosis in men: the DNASCO Study: a six-year randomized, controlled trial. *Ann. Intern. Med.* **140**, 1007–1014
- 65 Wildman, R. P., Schott, L. L., Brockwell, S., Kuller, L. H. and Sutton-Tyrrell, K. (2004) A dietary and exercise intervention slows menopause-associated progression of subclinical atherosclerosis as measured by intima-media thickness of the carotid arteries. *J. Am. Coll. Cardiol.* **44**, 579–585
- 66 Dinunno, F. A., Tanaka, H., Monahan, K. D., Clevenger, C. M., Eskurza, I., DeSouza, C. A. and Seals, D. R. (2001) Regular endurance exercise induces expansive arterial remodelling in the trained limbs of healthy men. *J. Physiol.* **534**, 287–295
- 67 Moreau, K. L., Silver, A. E., Dinunno, F. A. and Seals, D. R. (2006) Habitual aerobic exercise is associated with smaller femoral artery intima-media thickness with age in healthy men and women. *Eur. J. Cardiovasc. Prev. Rehabil.* **13**, 805–811
- 68 van Duijnhoven, N. T., Green, D. J., Felsenberg, D., Belavy, D. L., Hopman, M. T. and Thijssen, D. H. (2010) Impact of bed rest on conduit artery remodeling: effect of exercise countermeasures. *Hypertension* **56**, 240–246

- 69 Thijssen, D. H., Dawson, E. A., van den Munckhof, I. C., Tinken, T. M., den Drijver, E., Hopkins, N., Cable, N. T. and Green, D. J. (2011) Exercise-mediated changes in conduit artery wall thickness in humans: role of shear stress. *Am. J. Physiol. Heart Circ. Physiol.* **301**, H241–H246
- 70 Farpour-Lambert, N. J., Aggoun, Y., Marchand, L. M., Martin, X. E., Herrmann, F. R. and Beghetti, M. (2009) Physical activity reduces systemic blood pressure and improves early markers of atherosclerosis in pre-pubertal obese children. *J. Am. Coll. Cardiol.* **54**, 2396–2406
- 71 Meyer, A. A., Kundt, G., Lenschow, U., Schuff-Werner, P. and Kienast, W. (2006) Improvement of early vascular changes and cardiovascular risk factors in obese children after a six-month exercise program. *J. Am. Coll. Cardiol.* **48**, 1865–1870
- 72 Woo, K. S., Chook, P., Yu, C. W., Sung, R. Y., Qiao, M., Leung, S. S., Lam, C. W., Metreweli, C. and Celermajer, D. S. (2004) Effects of diet and exercise on obesity-related vascular dysfunction in children. *Circulation* **109**, 1981–1986
- 73 Skilton, M. R., Sieveking, D. P., Harmer, J. A., Franklin, J., Loughnan, G., Nakhla, S., Sullivan, D. R., Caterson, I. D. and Celermajer, D. S. (2008) The effects of obesity and non-pharmacological weight loss on vascular and ventricular function and structure. *Diabetes Obes. Metab.* **10**, 874–884
- 74 Olson, T. P., Dengel, D. R., Leon, A. S. and Schmitz, K. H. (2006) Moderate resistance training and vascular health in overweight women. *Med. Sci. Sports Exercise* **38**, 1558–1564
- 75 Jae, S. Y., Carnethon, M. R., Heffernan, K. S., Choi, Y. H., Lee, M. K. and Fernhall, B. (2007) Association between cardiorespiratory fitness and prevalence of carotid atherosclerosis among men with hypertension. *Am. Heart J.* **153**, 1001–1005
- 76 Palatini, P., Puato, M., Rattazzi, M. and Pualetto, P. (2010) Effect of regular physical activity on carotid intima-media thickness. Results from a 6-year prospective study in the early stage of hypertension. *Blood Press.* **20**, 37–44
- 77 Anderssen, S. A., Hjelstuen, A. K., Hjermann, I., Bjerkan, K. and Holme, I. (2005) Fluvastatin and lifestyle modification for reduction of carotid intima-media thickness and left ventricular mass progression in drug-treated hypertensives. *Atherosclerosis* **178**, 387–397
- 78 Watarai, T., Yamasaki, Y., Ikeda, M., Kubota, M., Kodama, M., Tsujino, T., Kishimoto, M., Kawamori, R. and Hori, M. (1999) Insulin resistance contributes to carotid arterial wall thickness in patients with non-insulin-dependent-diabetes mellitus. *Endocr. J.* **46**, 629–638
- 79 Kim, S. H., Lee, S. J., Kang, E. S., Kang, S., Hur, K. Y., Lee, H. J., Ahn, C. W., Cha, B. S., Yoo, J. S. and Lee, H. C. (2006) Effects of lifestyle modification on metabolic parameters and carotid intima-media thickness in patients with type 2 diabetes mellitus. *Metab. Clin. Exp.* **55**, 1053–1059
- 80 Trigona, B., Aggoun, Y., Maggio, A., Martin, X. E., Marchand, L. M., Beghetti, M. and Farpour-Lambert, N. J. (2011) Preclinical noninvasive markers of atherosclerosis in children and adolescents with type 1 diabetes are influenced by physical activity. *J. Pediatr.* **157**, 533–539
- 81 Seeger, J. P., Thijssen, D. H., Noordam, K., Cranen, M. E., Hopman, M. T. and Nijhuis-van der Sanden, M. W. (2011) Exercise training improves physical fitness and vascular function in children with type 1 diabetes. *Diabetes Obes. Metab.* **13**, 382–384
- 82 Okada, K., Maeda, N., Tatsukawa, M., Shimizu, C., Sawayama, Y. and Hayashi, J. (2004) The influence of lifestyle modification on carotid artery intima-media thickness in a suburban Japanese population. *Atherosclerosis* **173**, 329–337
- 83 Maiorana, A. J., Naylor, L. H., Exterkate, A., Swart, A., Thijssen, D. H., Lam, K., O'Driscoll, G. and Green, D. J. (2011) The impact of exercise training on conduit artery wall thickness and remodeling in chronic heart failure patients. *Hypertension* **57**, 56–62
- 84 Laughlin, M. H. (1995) Endothelium-mediated control of coronary vascular tone after chronic exercise training. *Med. Sci. Sports Exercise* **27**, 1135–1144
- 85 Tinken, T. M., Thijssen, D. H., Black, M. A., Cable, N. T. and Green, D. J. (2008) Time course of change in vasodilator function and capacity in response to exercise training in humans. *J. Physiol.* **586**, 5003–5012
- 86 Thijssen, D. H., Scholten, R. R., van den Munckhof, I. C., Benda, N., Green, D. J. and Hopman, M. T. (2011) Acute change in vascular tone alters intima-media thickness. *Hypertension* **58**, 240–246
- 87 Kozakova, M., Palombo, C., Morizzo, C., Nolan, J. J., Konrad, T. and Balkau, B. (2010) Effect of sedentary behaviour and vigorous physical activity on segment-specific carotid wall thickness and its progression in a healthy population. *Eur. Heart J.* **31**, 1511–1519
- 88 Kozakova, M., Palombo, C., Mhamdi, L., Konrad, T., Nilsson, P., Staehr, P. B., Paterni, M. and Balkau, B. (2007) Habitual physical activity and vascular aging in a young to middle-age population at low cardiovascular risk. *Stroke* **38**, 2549–2555
- 89 Okamoto, T., Masuhara, M. and Ikuta, K. (2006) Effects of eccentric and concentric resistance training on arterial stiffness. *J. Hum. Hypertens.* **20**, 348–354
- 90 Maiorana, A., O'Driscoll, G., Cheetham, C., Collis, J., Goodman, C., Rankin, S., Taylor, R. and Green, D. (2000) Combined aerobic and resistance exercise training improves functional capacity and strength in CHF. *J. Appl. Physiol.* **88**, 1565–1570
- 91 Maiorana, A., O'Driscoll, G., Dembo, L., Cheetham, C., Goodman, C., Taylor, R. and Green, D. (2000) Effect of aerobic and resistance exercise training on vascular function in heart failure. *Am. J. Physiol. Heart Circ. Physiol.* **279**, H1999–H2005
- 92 Langille, B. L. and O'Donnell, F. (1986) Reductions in arterial diameter produced by chronic decreases in blood flow are endothelium-dependent. *Science* **231**, 405–407
- 93 Ku, D. N., Giddens, D. P., Zarins, C. K. and Glagov, S. (1985) Pulsatile flow and atherosclerosis in the human carotid bifurcation. Positive correlation between plaque location and low oscillating shear stress. *Arteriosclerosis* **5**, 293–302
- 94 Zarins, C. K., Giddens, D. P., Bharadvaj, B. K., Sottiurai, V. S., Mabon, R. F. and Glagov, S. (1983) Carotid bifurcation atherosclerosis. Quantitative correlation of plaque localization with flow velocity profiles and wall shear stress. *Circ. Res.* **53**, 502–514
- 95 Ziegler, T., Bouzourene, K., Harrison, V. J., Brunner, H. R. and Hayoz, D. (1998) Influence of oscillatory and unidirectional flow environments on the expression of endothelin and nitric oxide synthase in cultured endothelial cells. *Arterioscler. Thromb. Vasc. Biol.* **18**, 686–692
- 96 Thijssen, D. H., Dawson, E. A., Tinken, T. M., Cable, N. T. and Green, D. J. (2009) Retrograde flow and shear rate acutely impair endothelial function in humans. *Hypertension* **53**, 986–992
- 97 Newcomer, S. C., Thijssen, D. H. and Green, D. J. (2011) Effects of exercise on endothelium and endothelium/smooth muscle crosstalk: role of exercise-induced hemodynamics. *J. Appl. Physiol.* **111**, 311–320
- 98 Laughlin, M. H., Newcomer, S. C. and Bender, S. B. (2008) Importance of hemodynamic forces as signals for exercise-induced changes in endothelial cell phenotype. *J. Appl. Physiol.* **104**, 588–600
- 99 Thijssen, D. H., Dawson, E. A., Black, M. A., Hopman, M. T., Cable, N. T. and Green, D. J. (2009) Brachial artery blood flow responses to different modalities of lower limb exercise. *Med. Sci. Sports Exercise* **41**, 1072–1079
- 100 Green, D. J., Bilsborough, W., Naylor, L. H., Reed, C., Wright, J., O'Driscoll, G. and Walsh, J. H. (2005) Comparison of forearm blood flow responses to incremental handgrip and cycle ergometer exercise: relative contribution of nitric oxide. *J. Physiol.* **562**, 617–628
- 101 Dinunno, F. A., Jones, P. P., Seals, D. R. and Tanaka, H. (2000) Age-associated arterial wall thickening is related to elevations in sympathetic activity in healthy humans. *Am. J. Physiol. Heart Circ. Physiol.* **278**, H1205–H1210

- 102 Tanaka, H., Dinunno, F. A., Monahan, K. D., DeSouza, C. A. and Seals, D. R. (2001) Carotid artery wall hypertrophy with age is related to local systolic blood pressure in healthy men. *Arterioscler. Thromb. Vasc. Biol.* **21**, 82–87
- 103 Pauletto, P., Scannapieco, G. and Pessina, A. C. (1991) Sympathetic drive and vascular damage in hypertension and atherosclerosis. *Hypertension* **17**, III75–III81
- 104 Roveda, F., Middlekauff, H. R., Rondon, M. U., Reis, S. F., Souza, M., Nastari, L., Barretto, A. C., Krieger, E. M. and Negrao, C. E. (2003) The effects of exercise training on sympathetic neural activation in advanced heart failure: a randomized controlled trial. *J. Am. Coll. Cardiol.* **42**, 854–860
- 105 Ray, C. A. and Hume, K. M. (1998) Sympathetic neural adaptations to exercise training in humans: insights from microneurography. *Med. Sci. Sports Exercise* **30**, 387–391
- 106 Ng, A. V., Callister, R., Johnson, D. G. and Seals, D. R. (1994) Endurance exercise training is associated with elevated basal sympathetic nerve activity in healthy older humans. *J. Appl. Physiol.* **77**, 1366–1374
- 107 Sugawara, J., Komine, H., Hayashi, K., Yoshizawa, M., Otsuki, T., Shimojo, N., Miyauchi, T., Yokoi, T., Maeda, S. and Tanaka, H. (2007) Systemic α -adrenergic and nitric oxide inhibition on basal limb blood flow: effects of endurance training in middle-aged and older adults. *Am. J. Physiol. Heart Circ. Physiol.* **293**, H1466–H1472
- 108 Minuz, P., Fava, C. and Cominacini, L. (2006) Oxidative stress, antioxidants and vascular damage. *Br. J. Clin. Pharmacol.* **61**, 774–777
- 109 Stocker, R. and Kearney, J. F. (2004) Role of oxidative modifications in atherosclerosis. *Physiol. Rev.* **84**, 1381–1478
- 110 Gomez-Cabrera, M. C., Domenech, E. and Vina, J. (2008) Moderate exercise is an antioxidant: upregulation of antioxidant genes by training. *Free Radical Biol. Med.* **44**, 126–131
- 111 Ait-Oufella, H., Taleb, S., Mallat, Z. and Tedgui, A. (2011) Recent advances on the role of cytokines in atherosclerosis. *Arterioscler. Thromb. Vasc. Biol.* **31**, 969–979
- 112 Ribeiro, F., Alves, A. J., Duarte, J. A. and Oliveira, J. (2010) Is exercise training an effective therapy targeting endothelial dysfunction and vascular wall inflammation? *Int. J. Cardiol.* **141**, 214–221
- 113 Chan, S. Y., Mancini, G. B., Burns, S., Johnson, F. F., Brozic, A. P., Kingsbury, K., Barr, S., Kuramoto, L., Schulzer, M., Frohlich, J. and Ignaszewski, A. (2006) Dietary measures and exercise training contribute to improvement of endothelial function and atherosclerosis even in patients given intensive pharmacologic therapy. *J. Cardiopulm. Rehabil.* **26**, 288–293

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