Chapter 5
Aerobic Exercise Training: Effects on Vascular Function and Structure

Dick H.J. Thijssen, Andrew Maiorana, and Daniel J. Green

Abbreviations

ACE	Angiotensin converting enzyme
ACh	Acetylcholine
ANG II	Angiotensin II
BP	Blood pressure
eNOS	Endothelial nitric oxide synthase
ET-1	Endothelin-1
FITT	The frequency, intensity, time, and type principle of exercise prescription
FMD	Flow mediated dilation
HITT	High intensity interval training
HR	Heart rate
ICAM-1	Intracellular adhesion molecule 1

D.H.J. Thijssen (✉)
Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, United Kingdom

Department of Physiology, Radboud University Medical Center, Nijmegen, The Netherlands
e-mail: dick.thijssen@radboudumc.nl

A. Maiorana
School of Physiotherapy and Exercise Science, Curtin University, Bentley, WA 6102, Australia

Advanced Heart Failure and Cardiac Transplant Service, Research Institute for Sport and Exercise Sciences, Royal Perth Hospital, Perth, WA 6102, Australia

D.J. Green
Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, United Kingdom

School of Sport Science, Exercise and Health, The University of Western Australia, Crawley, WA 6009, Australia

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IMT	Intima medial thickness
MAP	Mean arterial pressure
MCP-1	Monocyte chemotactic protein 1
MSNA	Muscle sympathetic nerve activity
NO	Nitric oxide
p22-phox	Neutrophil cytochrome b light chain
p47-phox	47-kDa cytosolic subunit of nicotinamide adenine dinucleotide phosphate
Q	Cardiac output
ROS	Reactive oxygen species
SNS	Sympathetic nervous system
SVR	Systemic vascular resistance
VO_{2max}	Maximum oxygen consumption

Introduction

Contemporary Westerners have reached an historical pinnacle of physical inactivity and further technological change is likely to exacerbate this [1]. Physical inactivity is an independent risk factor for atherosclerosis and cardiovascular diseases [2–4] and low cardiorespiratory fitness is a strong independent predictor of all-cause mortality [5]. Physical inactivity is a key factor in the etiology and progression of cardiovascular diseases, including hypertension. Regular physical exercise is associated with reduction in primary [6–9] and secondary vascular events [10, 11]. Meta-analyses, including those of exercise-based cardiac rehabilitation undertaken in the contemporary era, indicate that ~30 % exercise-related benefit is evident in terms of cardiac events relative to usual care [12]. This magnitude of benefit approximates or exceeds that associated with antihypertensive or lipid lowering medication interventions in large multicenter trials [13, 14], with a recent analysis concluding that exercise and drug interventions are similar in terms of their mortality benefits in secondary prevention [15]. These data indicate that exercise training and maintenance of physical fitness have important impacts on the prevalence and progression of cardiovascular disease, at least partly through changes in cardiovascular risk factors such as hypertension.

Purposes of this Chapter

This chapter discusses the impact of aerobic exercise training on the vasculature that may explain the blood pressure (BP) lowering effects of exercise training [16, 17]. We first provide an overview of the techniques use to assess

vasculature structure and function followed by relevant research regarding the influence of aerobic exercise training on vascular structure and function. The potential mechanisms that contribute to vascular adaptations to aerobic exercise are then discussed. Last, we integrate the available knowledge in this area to provide evidence-based guidelines for the benefits of exercise training on vascular health among individuals with hypertension. Please see related discussions to these topics in Chapters 1, 7–9.

Key Terminology and Basic Concepts

Aerobic Exercise

The term aerobic exercise training is typically used to refer to episodic whole-body exercise, characterised by use of the large muscle groups of the lower limbs (e.g., walking, running, cycling), sometimes combined with the upper extremities (e.g., rowing, swimming). It involves repeated dynamic muscular contractions that impact the cardiac and pulmonary systems, with marked increases in heart rate, ventilation and oxygen consumption. Most scientific literature has defined aerobic exercise as prolonged periods of exercise (>10 min) at moderate-to-high exercise intensity (60–80 % of the maximal heart rate). However, important differences exist between studies regarding the frequency (2–7 days per week), intensity (25–90 % of the maximal heart rate), time (30–60 min) and type (e.g. walking, running, cycling, rowing) of aerobic exercise training.

Vascular Functional and Structural Adaptations to Aerobic Exercise Training

Mean arterial pressure (MAP) is determined by cardiac output (Q) (derived by multiplying stroke volume [SV] and heart rate [HR]) and systemic vascular resistance [SVR] (MAP=Q×[SV×HR]×SVR). Studies in healthy subjects and those with hypertension have reported that aerobic training induces a decrease in heart rate (~10 %), which is counterbalanced by an increase in SV (~15 %), consequently leading to an unchanged or even slightly increased Q at rest. Given this preserved Q, the BP lowering effect of aerobic exercise training must be related to decreases in peripheral vascular resistance [18]. These changes in peripheral vascular resistance are mediated by functional and/or structural adaptations in the vasculature in conduit, resistance, *and* microvessels. In addition to the decrease in BP, improved vascular function and structure may also be related to decreased cardiovascular risk [19].

Techniques Used to Examine Vascular Structure and Function

How Is Artery Structure and Function Studied?

The in vivo assessment of arterial function and structure varies according to their size and functional classification. Conduit arteries have been defined as having a diameter: >1,000 μm, small arteries 300–1,000 μm, resistance arteries and arterioles diameter: 10–300 μm, and capillaries diameter: <6 μm [20]. In these terms, arteries that contribute substantively to vascular resistance and the systemic control of BP include small arteries, and resistance arteries and arterioles; henceforth collectively referred to in this ter as resistance vessels [20]. Below, we have discussed commonly adopted methods that are used to examine conduit and resistance artery vascular function and structure.

How Is Resistance Artery Structure and Function Studied?

Structure of Conduit Arteries (Diameter Assessment)

Echo-Doppler is used to assess the structure of conduit arteries. It allows for valid and reproducible assessment of resting diameters of nearly all superficial (<5 cm) conduit arteries in the upper and lower limbs, as well as the carotid arteries. Although resting diameter provides a surrogate measure of conduit artery structure in vivo, competing vasodilator and constrictor influences impact upon resting arterial tone. It has therefore been proposed that peak artery diameter, which represents a physiological capacity, may serve as a more valid structural index because it diminishes the impact of functional differences between subjects [21].

Structure of Conduit Arteries (Wall Thickness)

High-resolution ultrasound can also be used to assess conduit artery intima medial thickness (IMT) (Fig. 5.1), a surrogate measure of wall thickness. Atherosclerosis initially forms within these layers, and the assessment of IMT is therefore believed to reflect the presence of subclinical atherosclerosis. Nonetheless, it should be taken into consideration that the abundant presence of smooth muscle cells in the media layer of the arterial wall contributes to acute changes in IMT, under direct influence of vasodilator or vasoconstrictor substances [22]. Several studies have established that carotid IMT is associated with increased risk for adverse cerebral events (e.g., stroke) [23–27]. A larger carotid IMT is also associated with increased risk for cardiac (e.g., angina pectoris, myocardial infarction) [23, 25, 28–30] and peripheral vascular events (e.g., peripheral artery disease, hypertension) [31, 32]. 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 [33], highlighting the clinical significance of IMT. Studies

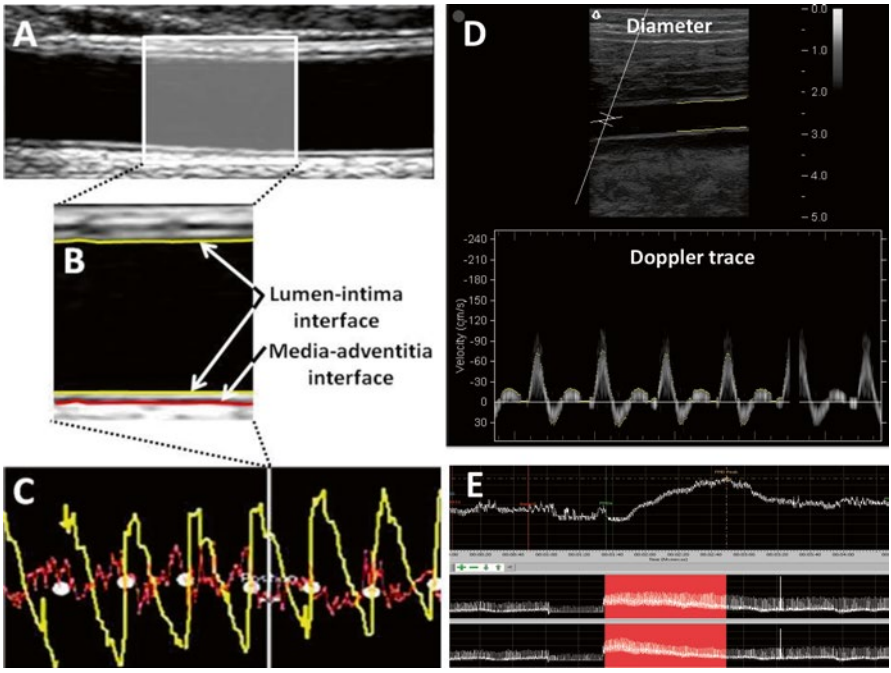

Fig. 5.1 Assessment of conduit artery structure and function. Ultrasound image of a carotid artery (**a**) from a healthy subject. Clearly demarked lines represent the lumen–intima interface (*yellow line*) and media–adventitia interface (*red line*, **b**), that are used to assess the intima-media thickness of a conduit artery. These images are then used to examine the change in diameter (*yellow line* to *yellow line*) and intima-media thickness (*yellow line* far wall to *red line* far wall) across the cardiac cycle. (**c**) Ultrasound image of a brachial artery (**d**) of a healthy subject, combined with a Doppler tracing of the red blood cell velocity in the same vessel. Based on the clearly demarked lines on the artery wall and from the Doppler trace (both *yellow lines*) in figure **d**, changes in diameter and blood velocity is presented across time (**e**). This allows for the identification of the peak diameter after cuff occlusion (i.e. *red area*) as a measure of vascular function

proposed that the annual change in IMT, rather than the carotid IMT itself, could be a stronger predictor for future events. However, a recent meta-analyses found no predictive effect of the *annual change* in carotid artery IMT [34], which also highlights the technical difficulty of measuring small changes in arterial wall thickness with current ultrasound techniques.

Function of Conduit Arteries (Endothelial Function)

In conduit arteries, endothelium-dependent vasodilator function is assessed by high resolution ultrasound following an increase in blood flow, which triggers shear stress-mediated vasodilation [35]. This technique is commonly referred to as the

flow mediated dilation (FMD). The dilation is at least partly mediated by nitric oxide (NO) [36–39], and serves as a valid index of conduit artery endothelium-dependent NO function [40]. FMD is often performed in the brachial artery, where it is demonstrated to be correlated with coronary endothelial function [41, 42]. Moreover, the brachial artery FMD has independent predictive capacity for future cardiovascular events [43–45]. These studies found that a 1 % increase in brachial artery FMD is associated with a 13 % reduction in cardiovascular risk in subjects at increased cardiovascular risk [43], while a 1 % change in FMD is associated with a 4 % change in cardiovascular risk in healthy, asymptomatic subjects [44].

How Are Resistance Artery Structure and Function Studied?

Structure of Resistance Arteries

Peripheral resistance vessel structure in humans has traditionally been assessed from measurement of the hyperemic (blood flow) response to a maximal vasodilator stimulus [46–48]. The conceptual basis for this approach is that assessment of resting blood flow reveals little information regarding the collective cross-sectional area of the resistance vessel bed, because of confounding and competitive influences of vasodilator and constrictor stimuli on basal tone. In contrast, measurement of blood flow in response to a vasodilator stimulus that elicits maximal or peak vasodilation provides insight into the capacity of the resistance vessel bed in question. In this context, peak reactive hyperemia after 10 min of limb ischemia induced by cuff inflation cannot be significantly increased by co-infusion of vasodilator agents [46]. Assessment of peak blood flow responses historically involved plethysmographic blood flow measurement [49], however, Doppler ultrasound methodology has recently been applied [21].

Function of Resistance Arteries

Vascular function of the resistance vessels can be examined by constructing dose–response curves to intra-arterial infusion of vasoactive substances. Blood flow is assessed using plethysmographic approaches to detect changes in limb volume, or direct conduit artery imaging using duplex ultrasound. Evaluating the responses to endothelium-dependent and -independent vasodilators provides information about the impacts, in vivo, of exercise training on specific dilator pathways [50, 51].

Methods

We summarized papers that examined the impact of aerobic exercise training on BP in healthy asymptomatic subjects and subjects with pre- and established hypertension. Using PubMed as our primary search engine, we searched for papers that

involved aerobic exercise training ('exercise training OR aerobic training OR aerobic exercise training OR endurance training OR endurance exercise training'). We excluded papers that used alternative modes of exercise and/or combined aerobic exercise training with (high-intensity) resistance exercise training. To specifically discuss the effects of aerobic training in hypertension, we combined the search strategy as stated above with 'hypert* OR pre-hypert* OR prehypert* OR high blood pressure'. The effects of aerobic training on BP are largely explained through changes in the vasculature. Therefore, to better understand the impact of aerobic exercise training on BP regulation, we expanded our search to studies that explored the impact of aerobic training on conduit and resistance arteries.

Relevant Research

Effect of Aerobic Exercise Training on Vascular Structure

Conduit Artery Diameter

Several cross-sectional and longitudinal studies suggest that aerobic training is associated with enlargement of skeletal muscle conduit arteries in humans. In an early study, it was observed that (predominantly) aerobic-trained athletes have increased resting diameters in large arteries (i.e., aorta, carotid, subclavian arteries) relative to matched sedentary controls [52]. These differences persisted after correction for body surface area between groups. In contrast, wheelchair athletes demonstrated enhanced dimensions in the aortic arch and subclavian artery, but lower values in the abdominal aorta and mesenteric artery [53]. These findings essentially extended previous reports of enlargement in conduit arteries of endurance-type athletes compared to control subjects [54, 55].

Recently, conduit artery diameter was examined in dominant and non-dominant limbs of different types of athletes, including wheelchair athletes [56, 57]. This series of studies revealed the largest brachial artery diameter in athletic groups who were primarily engaged in upper limb dominant exercise (i.e., canoeists and kayakers). More specifically, a within-subject comparison performed between the dominant and non-dominant brachial arteries of elite squash players revealed a localized outward remodeling of the dominant brachial artery. These findings suggest the presence of localized adaptation of diameter in response to exercise training.

In studies of healthy, young men, significant increases in the dimensions of the ascending and abdominal aorta were observed following 8 weeks of cycle ergometer training [58]; and of the femoral artery in the trained, but not untrained limb, after 6 weeks of one-legged cycle exercise [59]. These training effects were reversed following detraining [59]. More recently, Spence et al. performed a 6 month exercise training study to assess the effect of aerobic exercise training in healthy male subjects on brachial, femoral, and carotid artery diameter [60]. While no improvements were observed in brachial and carotid artery diameter, a significant and marked increase was observed in femoral artery resting diameter. These observations

Table 5.1 Summary of the initial (0–4 weeks) and long-term (>8 weeks) changes in conduit artery function (i.e. flow-mediated dilation (FMD)) and structure (i.e. diameter (D) and intima-media thickness (IMT)) and resistance artery function (i.e. intra-brachial infusion of endothelium-dependent and independent vasoactive substances) and structure (i.e. peak blood flow (BF_{peak})) in the active area and non-active area in response to endurance exercise training

		Active area		Non-active area	
		Initial change	Long-term change	Initial change	Long-term change
Conduit artery	Function (FMD)	↑	↑/↔[a]	↑	↑/↔[a]
	Structure (D)	↔	↑	↔	↔
	Structure (IMT)	↔	↓	↔	↓
Resistance artery	Function (invasive)	↑	↑/↔[a]	↑	↑/↔[a]
	Structure (BF_{peak})	↔	↑	↔	↑

[a]The size and direction of the effect size may differ between healthy subjects (↔) and subjects with cardiovascular disease/risk (↑)

strongly support the ability of aerobic training to result in outward remodeling of conduit arteries, leading to larger conduit artery diameters in healthy subjects [60]. Moreover, this process in healthy young subjects is rapid and depends on local, rather than systemic factors (Table 5.1).

Conduit Artery Wall Thickness

Cross-sectional studies on the impact of aerobic exercise training on carotid artery IMT in healthy subjects have reported conflicting results. For example, several studies found no significant difference in carotid IMT between trained subjects and sedentary controls in young, middle aged, or older cohorts [61–63]. These findings are supported by studies involving aerobic training in sedentary subjects that found no effect of 8–12 weeks of aerobic exercise training on carotid IMT [61, 64, 65]. A more recent study, however, found a significantly lower carotid artery IMT in elite squash players compared with less active controls [56]. The difference in training intensity and/or load may explain these disparate results, as elite squash players exercised >22 h per week at high intensity [56], while others studies involved aerobic training (cross-sectional and longitudinal studies) exercising >3 h per week [62] or >5 days per week [61, 63].

A limited number of cross-sectional studies have examined the effect of aerobic exercise training on the wall thickness of the peripheral arteries. In contrast to findings in the carotid artery, lower femoral artery IMT was observed in aerobic trained men and women compared with their sedentary peers [66, 67]. Also, when studying elite athletes (i.e., squash players), a lower peripheral artery IMT was found in the femoral and brachial arteries compared to their sedentary controls [56]. Studies that adopted longitudinal training designs also reported smaller IMT of peripheral conduit arteries after 12–24 weeks of aerobic training [66, 68]. Taken together, aerobic training studies performed in healthy, predominantly Caucasian subjects indicate that aerobic exercise training leads to a smaller IMT in peripheral arteries supplying the active skeletal muscle (Table 5.1).

In subjects with cardiovascular risk factors, such as hypertension, an *a priori* increased IMT is typically found in the carotid and peripheral vessels. This finding potentially allows for marked effects of aerobic exercise training in these subjects [69]. In individuals with hypertension, an inverse relationship was present between cardiorespiratory fitness and carotid artery atherosclerosis (defined as a wall thickness >1.2 mm) [70]. Another study in subjects with hypertension demonstrated that higher self-reported physical activity was associated with a lower 6.5 year increase in carotid IMT [71]. Although these between-subject studies suggest that training is associated with a smaller IMT in subjects with hypertension, no study has directly examined the effect of aerobic training on carotid or peripheral artery IMT.

Resistance Arteries

Sinoway et al. performed two of the earliest studies which specifically addressed the impact of aerobic training on resistance vessel "structure" in healthy subjects. By using a stimulus that induced peak dilation, without inducing reflex changes in vasomotor control, they sought to assess the effect of aerobic exercise training on structural resistance artery adaptation. Sinoway and colleagues demonstrated that the preferred limbs of tennis players exhibit higher peak vasodilator responses than the non-preferred limbs of these athletes or either limb of non-tennis playing control subjects [72]. This finding was later confirmed in elite tennis players [73]. Comparable effects of an enhanced maximal peak blood flow have been reported after different types of aerobic exercise training across a large age range [74–76]. In subjects with hypertension, who demonstrate lower *a priori* peak dilator responses, aerobic exercise training increases forearm peak blood flow [77].

The enhanced intrinsic vasodilator capacity of active muscle beds following training may conceivably result from the well-established increase in capillary density that occurs with training [78]. However, muscle blood flow is not dependent upon capillary density [79]. While capillaries regulate transit time and oxygen extraction, they contribute much less resistance to flow than upstream arterioles [20, 80, 81]. Electrical stimulation studies suggest that the time-course of adaptation in capillary density (~4 days) [82] is dissociated from adaptations in peak blood flows (14–28 days) [83]. Adaptations in peak blood flow with training, therefore reflect changes in the caliber or cross-sectional area of the "resistance arteries", rather than increases in capillarity

Summary of the Impacts of Aerobic Exercise Training on Arterial Structure

In summary, aerobic exercise training represents a potent stimulus for conduit and resistance arteries to adapt. More specifically, aerobic exercise training in healthy, predominantly Caucasian subjects leads to larger conduit artery diameters and smaller conduit artery IMT. Conduit artery remodeling represents a

process that depends on a localized process in the active limbs; while the decrease in IMT is observed in the active and non-active limbs, suggesting the presence of a systemic effect of aerobic exercise training on IMT. Finally, aerobic exercise training also leads to enlargement of the resistance arterial vascular bed, a localized process that occurs in active limbs. These structural adaptations may contribute to the benefits of exercise training on BP. While a larger resistance arterial bed can lower peripheral resistance, and therefore BP, it should be acknowledged that remodeling of conduit arteries unlikely play an important role in peripheral vascular tone.

Effect of Aerobic Training on Vascular Function

The function of conduit and resistance vessels reflects the balance between competing effects of vasodilator and vasoconstrictor influences. Discussion of vascular function will primarily focus on the impact on NO bioavailability, given its important role as a vasodilator as well as its anti-atherosclerotic and anti-thrombotic effects. Studies examining vasoconstrictor pathways have focussed on endothelin-1 (ET-1) and angiotensin II (ANG II), arguably the most important vasoconstrictors, and the sympathetic nervous system (SNS).

Vasodilator Function

Conduit Arteries

A number of studies have examined the effects of aerobic training on conduit artery vascular function using FMD. In healthy subjects, improvement in conduit artery FMD is not a generalised finding [64, 84]. In contrast, aerobic training undertaken in subjects with *a priori* impairment in conduit artery endothelial function typically demonstrate enhanced FMD responses after aerobic exercise training [85, 86]. Indeed, studies undertaken in subjects with hypertension [87, 88], who exhibit endothelial dysfunction, demonstrate enhanced FMD responses following different aerobic training programs. Given the conflicting results of aerobic exercise training on conduit artery FMD in subjects with normal BP, one may question whether individuals with prehypertension benefit from aerobic training. Interestingly, significant improvement in brachial artery FMD after prolonged (12 weeks) aerobic exercise training was found in subjects diagnosed with Stage I hypertension (or prehypertension), but not in subjects with normal BP [87]. Therefore, conduit artery function appears more amenable to enhancement in subjects with pre to established hypertension, who exhibit impaired vasomotor and endothelial function *a priori*, than in healthy subjects with less impaired vascular function prior to training.

Resistance Arteries

The impact of aerobic exercise training in healthy control subjects has frequently been studied in resistance arteries using plethysmography. In young subjects who undertook aerobic cycle exercise training, improvement in basal NO function was observed, but no changes in endothelial function were apparent [89]. Despite the improvement in NO bioavailability in this study, no changes in basal limb blood flow were found after training, possibly because of a compensatory increase in sympathetic vasoconstrictor tone [90].

Consistent with the case for conduit artery function (above), there is no apparent consensus regarding the impact of aerobic training on resistance vessel function in healthy (young) subjects; whereas the majority of studies performed in subjects with impaired endothelial function have documented improvement. For example, aerobic exercise training in middle aged subjects enhanced endothelial function [91, 92] and improved NO bioavailability [90]. Furthermore, 12 weeks of aerobic exercise training in subjects with hypertension improved peripheral resistance artery endothelial function [77, 92].

Several important studies have indicated a beneficial impact of aerobic training on coronary vasodilator function among patients with coronary artery disease [93–95] and heart failure [96]. For example, Hambrecht and colleagues studied 19 patients with stable coronary artery disease that were randomised to aerobic training or control groups for a 4 week period [95]. Intra-coronary infusion of acetylcholine (ACh) and adenosine were used to assess epicardial coronary artery vasodilator function and resistance vessel function, respectively. Training improved coronary conduit and resistance artery vasodilator function. In a subsequent study, the authors found that home-based aerobic training sustained some of these effects [97]. These authors also completed a comprehensive study which concluded that aerobic training improves vasodilator function in vivo by upregulating NO synthase protein expression and by increasing phosphorylation of NO synthase, effects consistent with a shear-stress mechanism for enhanced NO bioactivity with training [94]. Taken together, these findings strongly support the presence of an improvement of resistance artery vascular function after aerobic exercise training in subjects with cardiovascular disease or risk (Table 5.1).

Vasoconstrictor Function

When studying the contribution of ET-1 and Ang II to the regulation of baseline vascular tone, studies have found that these constrictors do not importantly contribute to the regulation of baseline resting tone in healthy, young subjects [98–100]. It is therefore unlikely that aerobic exercise training in healthy subjects importantly alters vasoconstrictor function. In contrast, older humans exhibit increased ET-1-mediated vascular tone in the leg [101] and forearm [102]. More importantly, aerobic training is able to reverse the contribution of ET-1 to baseline

vascular tone in older humans [101, 102]. Regarding Ang II, aerobic exercise training in patients with stable coronary artery disease induced a 49 % reduction in Ang II-induced vasoconstriction [103]. While the evidence relating to aerobic training effects on vasoconstrictor pathways is far less comprehensive than that for vasodilator mechanisms, aerobic exercise training seems to have a beneficial effect on vasoconstrictor pathways in those with an *a priori* increased contribution of vasoconstrictors to vascular tone.

The question of whether neurally-mediated vasoconstriction is modified by aerobic 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, is improved by aerobic training [104–106] and is related to physical activity levels [107] (see Chapter 9 for a more detailed discussion of the effects of exercise on autonomic function). Other studies suggest that noradrenaline levels diminish following training [108]. In keeping with these findings, training ameliorates the effect of aging on baroreflex function [109], an effect which may be related to enhanced arterial vasodilator function, arterial distensibility, and signal transduction in barosensitive zones [110]. In addition, muscle sympathetic nerve activity (MSNA) may decrease as a result of aerobic training [111] including subjects with elevated SNS activity *a priori* [112]. Finally, repeated bouts of exercise are associated cyclic activation of brainstem centres, such as the rostral ventrolateral medulla, may modulate central sympathetic output and SNS mediated vasoconstriction [113]. These studies suggest that sympathetic nerve mediated vasoconstrictor tone may decrease as a result of aerobic training in humans.

However, there is also evidence to the contrary. Studies performed in healthy subjects suggest that MSNA does not change with training [112] and noradrenaline spill-over may also be similar following training when expressed in relative terms [114]. In addition, α-adrenoceptor blockade (i.e., a direct measure to examine the role of the SNS), revealed an increased level of basal sympathetic vasoconstrictor tone following aerobic training in healthy volunteers [90], consistent with other evidence of elevated basal sympathetic tone following training [115]. Despite this apparent increase in resting sympathetic tone, basal blood flows are not decreased by training, a finding likely due to a compensatory increased vasodilator function or remodelling. Hence, 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, there is evidence in coronary arteries consistent with elevated basal vasoconstriction tone in trained subjects who also possessed enlarged arteries [116].

Specifically for individuals with hypertension, relatively few studies have focused on the impact of aerobic training on the SNS. A previous report examined the impact of a 4 month, pre-dominant lower limb aerobic exercise training on baroreflex control of MSNA in (never-medicated) patients with hypertension [117]. The drop in BP after training was accompanied by a drop in MSNA level as well as a significant improvement in baroreflex control during BP manipulations in these subjects. Interestingly, the authors even reported a significant positive relation between the decrease in resting MSNA and the drop in MAP.

In summary, evidence in humans suggests that aerobic training can improve the contribution of ET-1 and ANG II in the regulation of vascular tone in those with *a priori* elevated contribution of vasoconstrictors to regulate vascular tone. In addition, some evidence suggests that aerobic training has a direct effect on the SNS, most likely resulting in improvement in baroreflex sensitivity and attenuation of the contribution of the SNS to the regulation of vascular tone in those with an *a priori* elevation in SNS tone. A smaller contribution of vasoconstrictor pathways to regulate tone after periods of training may represent a key mechanism contributing to the BP lowering effect of exercise training.

Time Course of Vascular Functional–Structural Adaptation

Although aerobic exercise training alters both conduit and resistance vessel function and structure, the time-course of these changes likely differs. In animals, short duration aerobic exercise training (2–4 weeks) improved vasodilator function in muscle arterioles [118, 119] and the aorta [120, 121]. Also in conduit vessels, improved vasodilator function has been observed after short duration aerobic exercise training (i.e., 7 days) [122]. These findings suggest that improved vascular *function*, demonstrated by an increased production of endothelial NO, occurs rapidly in response to aerobic training, particularly in arteries supplying the exercising muscle beds [123].

Animal studies performed over a longer duration have not consistently shown augmented endothelial function in healthy animals. Endothelium-dependent vasodilation was unaltered after 16–20 weeks of training in pigs [124] and 16 weeks in rats [125]. There is also evidence that endothelial nitric oxide synthase (eNOS) expression is time-dependent. Expression of eNOS protein and enhanced vasodilator function [126] were evident after 1 week of training in pigs, whereas these changes were not present after 16 weeks [127]. Although these data suggest that long-term training is not consistently associated with enhanced vasodilator function, prolonged aerobic training enlarges arterial diameters in animals [128–131]. Laughlin proposed, on the basis of these animal data, that a distinct time-course for change in arterial function and structure may exist in response to exercise training [123]. These data in animals resulted in the hypothesis [86] that, in humans, vascular remodelling, an endothelium and NO-dependent phenomenon [132–137], may partly supplant the need for acutely responsive vasodilator mechanisms to normalise shear stress during exercise bouts [86].

Recently, Tinken et al. completed a study in which measures of brachial and popliteal artery function and structure were collected every 2 weeks across an 8 week aerobic training program in healthy, young male subjects [138]. The results indicated that functional adaptation preceded changes in artery peak vasodilator capacity. These findings support the notion that functional adaptations may be superseded by structural changes including artery remodelling that may normalise shear stress. They confirm previous reports that endothelial function rapidly adapts

to training and detraining [139, 140]. Moreover, others have now confirmed the time-dependent changes in conduit artery function in healthy subjects during aerobic exercise training [141].

In summary, animal studies suggest that short-term aerobic training enhances eNOS and NO production and bioactivity, producing a short-term buffer to the increased shear associated with exercise. With continued training, at least in the peripheral circulation, structural changes in the vessels occur, resulting in an increase in lumen diameter [20, 135]. Whether a similar time-course in vascular adaptations is present in subjects with pre and established hypertension is currently unknown. Furthermore, little is known whether the distinct time-course in functional and structural vascular adaptations lead to a time-course in adaptation of BP or BP control.

Local Versus Systemic Adaptations

An important question for prescribing aerobic exercise training is whether such exercise leads to local or systemic adaptations in the vasculature. This question is of particular importance when exercise is prescribed with the aim of modulating BP, which requires systemic adaptation in vascular resistance. Studies that have investigated the impact of lower limb aerobic exercise training on vascular function in humans typically found improvement in upper limb vascular function [89, 91, 92, 142–144]. Hence, the vast majority of studies that examined the impact of aerobic exercise training reveal systemic improvements in vascular function in conduit and resistance vessels (Table 5.1).

In terms of generalized effects of training on vascular *structure*, results depend upon the vascular territory examined. It is well established that aerobic training leads to an outward remodeling of conduit artery diameter which supply the active muscle beds. For example, brachial diameters are significantly larger in elite canoe paddlers and wheelchair athletes, compared to control subjects, while superficial femoral artery diameters are significantly larger in runners and cyclists than controls and paraplegic subjects [57]. In addition, the dominant and non-dominant arms of elite tennis players differ in terms of conduit and resistance artery remodelling [53, 73], a finding reinforced by observation of larger racquet arm brachial diameters in elite squash players [56]. Aerobic exercise training, despite its strong and systemic stimulus, therefore seems to result in a local impact on conduit artery diameter remodelling. There is little extant evidence for remodelling of artery size in vessel beds outside those involved directly in the exercise stimulus.

Information regarding the impact of aerobic exercise training on local or systemic adaptations in wall thickness is scarce. Most studies that examined the impact of aerobic exercise training have adopted cross-sectional comparisons. Rowley et al. assessed carotid, brachial, and superficial femoral artery wall thickness in elite athletes engaged in predominantly lower limb (i.e., runners/cyclists) or upper limb (i.e., canoe paddlers) exercise and matched able bodied, recreationally active, controls. In this study, wheelchair controls and athletes were also studied to further

examine the impact of aerobic training on arterial wall thickness. Diminished wall thickness was observed in all arteries of able bodied athletes compared to controls, including wheelchair athletes compared to wheelchair controls [57]. A further study of elite squash players also confirmed decreased brachial artery wall thickness, which in contrast to the effects on lumen diameter, was apparent in *both* limbs [56]. This finding suggests that aerobic exercise training results in changes in wall thickness in athletes, which may be a systemic phenomenon. In support of this notion, longitudinal training studies suggest that peripheral arterial wall thickness decreases after lower limb aerobic exercise training in femoral [66], popliteal, and brachial [68, 145] arteries. Although limited in scope, these data support the presence of systemic changes in conduit artery wall thickness after aerobic exercise training.

In summary, aerobic exercise training represents a potent stimulus for systemic adaptations in conduit and resistance artery function, but also for systemic improvements in conduit artery wall thickness (but not diameter) and resistance artery structure (Table 5.1). These findings suggest that aerobic exercise training leads to beneficial changes in vascular function and structure beyond the active vascular bed, assuming a sufficiently large active muscle mass is activated. The presence of systemic vascular adaptation after large muscle activity is of special importance for BP lowering, as lowering of total peripheral vascular tone is an important pathway to explain the benefits of exercise training on BP.

Mechanisms Responsible for Arterial Adaptation to Aerobic Exercise Training

Shear Stress

Exercise produces large increases in blood flow to the heart and active skeletal muscle [146]. These increases in blood flow during exercise generate shear forces that act on the endothelium that alter gene expression in endothelial and vascular smooth muscle cells [147–149]. The beneficial effects of exercise on vascular health have often been attributed to exercise-induced increases in mean shear stress [150–153]. This hypothesis is supported by data obtained from cell culture and isolated vessel preparations which demonstrate that increased shear stress positively modifies the expression of genes involved in the atherosclerotic process [154–159]. The impact that shear stress has on gene expression is highlighted by reports that increases in shear stress change the expression of approximately 3,000 cultured endothelial cell genes as assessed by microarray analysis [160].

The limited data obtained from in vivo models also support the notion that increases in mean shear stress provide a stimulus that is anti-atherogenic. Specifically, increases in shear stress, produced by arteriovenous fistulas in rats and dogs, have been reported to increase messenger ribonucleic acid (mRNA), protein, and activity of eNOS and decrease bioavailability of ET-1 [151, 152]. In humans, unopposed increases in retrograde shear stress acutely impair endothelial function

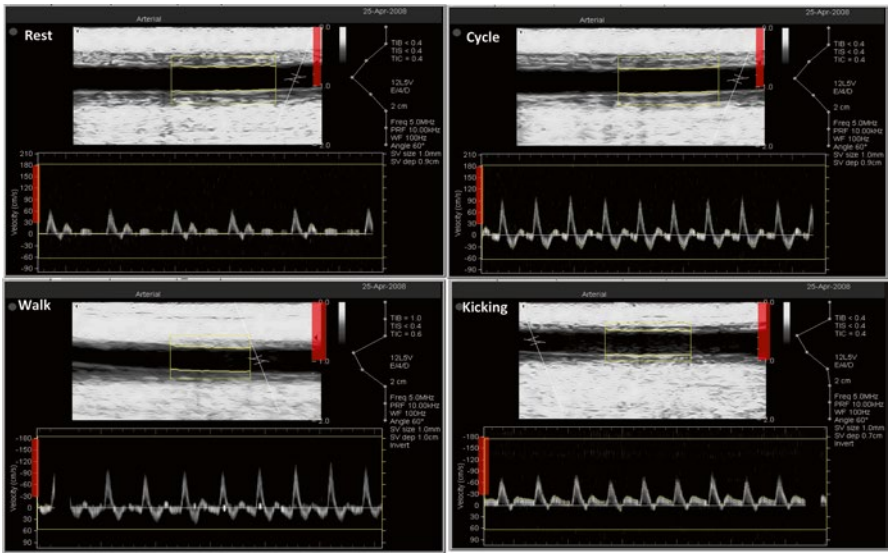

Fig. 5.2 Blood flow patterns during exercise. Echo-Doppler images from the brachial artery diameter and blood flow pattern under resting conditions (**a**), leg cycling exercise (**b**), walking exercise (**c**), and leg kicking exercise (**d**). Note the marked differences in blood flow patterns between the four different conditions

[161, 162], while some evidence suggests that increases in antegrade shear are associated with enhanced FMD [141, 163, 164]. See Chapter 7 for more detailed information about the effects of the application of in vitro shear stress on endothelial cell gene expression.

Data linking increases in mean shear stress to atheroprotective changes in gene expression has focused attention on mean shear as a modulating stimulus. However, it is important to acknowledge that the pattern of the hemodynamic profile seems to play an import role. This notion is supported by observations regarding significant changes in the pattern of shear when transitioning from rest to exercise [165] (Fig. 5.2). During the initial phase of lower limb aerobic exercise (such as cycling), the pattern of brachial artery blood flow through the conduit arteries becomes more oscillatory in nature, resulting in both the antegrade (i.e., forward) and retrograde (i.e., backward) components of blood flow. It is believed that the increase in retrograde component of the blood flow pattern during the initial phase of exercise is mediated through an increase in peripheral artery resistance [166], perhaps as a consequence of the activation of the SNS.

The initial increase in retrograde flow and shear stress, and therefore, oscillatory shear does not necessarily indicate that exercise leads to potentially harmful effects on the endothelium. Recent data demonstrate that changes in the pattern of blood flow through conduit arteries are subject to change as exercise continues [167]. The favorable shear pattern of largely antegrade shear during prolonged exercise is associated with beneficial adaptation in the vessels. Hambrecht and colleagues provided

an insight into the mechanisms responsible for exercise-mediated improvements in endothelial function [94]. They studied the impact of 4 weeks of cycle exercise on the internal mammary artery of subjects with coronary artery disease awaiting coronary artery bypass surgery. Training increased peak endothelium-dependent flow and FMD responses in the arteries of trained subjects, but not sedentary controls. After the final training session and the repeat in vivo vascular function assessments, a section of the internal mammary artery was harvested for in vitro vascular function assessment, immunohistochemistry, NO synthase mRNA isolation, and protein quantification. Aerobic training was associated with significantly higher NO synthase mRNA and protein expression and higher shear stress related eNOS phosphorylation, which correlated with in vivo ACh mediated vasodilator capacity. Aerobic training therefore improves endothelial function in vivo by upregulating NO synthase protein expression and by increasing phosphorylation of this enzyme, effects consistent with a shear stress mechanism for enhanced NO bioactivity with training.

More recently, to examine the suggestion that shear is a key mechanism responsible for changes in endothelium-mediated vasodilator function following aerobic training, subjects performed a single bout of cycle exercise [163]. During the exercise session, a cuff was placed around one arm to unilaterally decrease the exercise-induced elevation in blood flow and shear stress [163]. While vasodilator function improved immediately after exercise in the limb exposed to increases in shear stress, no changes were observed in the cuffed arm. To follow-up on this observation, we adopted the same model (i.e., unilateral cuff inflation to attenuate the exercise-induced blood flow and shear stress response) and performed 8 weeks of cycle exercise training [141]. We found significant, time-dependent changes in vasodilator function and structure of the brachial artery in the non-cuffed arm, while such adaptations were non-existing in the cuffed arm. Taken together, these data resulted in the conclusion that shear stress is a principal physiological stimulus to the vascular adaptation associated with aerobic training in vivo.

In order to confirm the importance of shear stress, independent of the complex stimulus of exercise, subsequent studies induced repeated episodic increases in shear stress at rest, using heating. As above, 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 [168, 169]. We found that these adaptations occur in response to repeated exposure to *direct* (local) application of heat to the arm by submerging arms in a warm water [169], but also by repeated exposure to systemic heating by submerging the lower limbs in warm water which elevates upper limb shear rate through systemic thermoregulatory adjustments [170]. These findings suggest that increases in shear, independent on the method of inducing elevation in shear, can induce adaptation of vessels.

The majority of studies demonstrate an important role for the increase in shear stress in inducing structural vascular adaptation in response to aerobic exercise training. The classic study of Langille and O'Donnell established a link between changes in flow (or shear) and the endothelium to induce arterial remodelling [134].

They examined rabbit carotid arteries after unilateral ligation-mediated chronic decreases in flow (70 % reduction for 2 weeks). The diameter of the ligated vessel was significantly smaller than the contralateral control vessel; and this change was dependent upon the endothelium, inferring that flow-mediated changes in vessel structure are dependent upon the release of a substance from endothelial cells.

Taken together, the above data are consistent with the evolving hypothesis that arterial shear stress is a homeostatically regulated variable and plays a pivotal role in adaptations of the vascular bed in response to aerobic exercise training [86, 171]. In this conceptual framework, shear stress mediated arterial enlargement, which acts to mitigate the increases in transmural pressure and wall stress brought about by repeated exercise bouts [135, 172–177], and is dependent on an intact endothelium [134]. The consequent "structural" normalization of shear may obviate the need for ongoing and acute functional adaptations [85, 86]. This hypothesis [86] clearly fits with the time-course of changes in vascular function and structure, as described in an earlier paragraph in this chapter.

Cyclic Pressure

Increases in blood flow during aerobic exercise are also accompanied by significant increases in pulse pressure. This elevation in pressure across the cardiac cycle produces an increase in the rhythmic stretching (i.e., cyclic strain) of endothelial and vascular smooth muscle cells across the vasculature. The systemic nature of cyclic strain makes it an attractive mechanism for describing how aerobic exercise training positively impacts vascular adaptation, especially given the systemic nature of vascular adaptations to this type of exercise.

Data initially obtained from in vitro cell culture preparations suggested that cyclic strain produced an anti-atherogenic endothelial cell phenotype through the upregulation of eNOS mRNA, protein, and enzyme activity [178, 179]. In contrast, other experiments reported that cyclic strain did not change eNOS mRNA expression in cultured endothelial cells [159, 180]. The lack of changes in eNOS expression in addition to reported increases in monocyte chemotactic protein 1 (MCP-1) [181], intracellular adhesion molecule 1 (ICAM-1) [182–184], ET-1 [159], E-selectin [182], and reactive oxygen species (ROS) production [181, 184] suggests that cyclic strain likely produces a pro-atherogenic phenotype in cultured endothelial cells. More recent data obtained from isolated vessel preparations suggest that reducing the cyclic strain stimulus decreases the phosphorylation of serine 1177 on eNOS and increases ROS production through the upregulation of neutrophil cytochrome b light chain (p22-phox) and 47-kDa cytosolic subunit (p47-phox) of nicotinamide adenine dinucleotide phosphate [185].

The discrepancy in results obtained from endothelial cell culture and isolated whole vessel preparations cannot be accounted for by the presence of vascular smooth muscle in the later experimental paradigm, given that cyclic strain increases ROS production and MCP-1 in smooth muscle cell culture [186, 187]. One might speculate that reported differences between data obtained in endothelial and smooth

muscle cell culture versus whole vessel preparations may reflect the necessary cross talk between endothelial and vascular smooth muscle cells in producing an anti-atherogenic phenotype when exposed to a cyclic strain stimulus. Future research using cocultured endothelial and vascular smooth muscle cells will be required to determine if cross talk between endothelial and smooth muscle cells produces an anti-atherogenic cell phenotype in response to cyclic strain.

In humans, it is extremely difficult to selectively examine the impact of cyclic strain and repetitive increases in BP on the vasculature as each change in pressure will be associated with a change in blood flow and shear rate. This is probably an important reason why studies in humans have not attempted to specifically address the role of cyclic strain on the exercise-induced vascular adaptations. Although further studies are required, cyclic strain may be a potentially important stimulus for the arteries to adapt in response to aerobic exercise training.

Clinical Implications and Importance

Exercise Prescription Recommendations for Vascular Health Among Individuals with Hypertension

Prescribing exercise training to subjects with hypertension cannot be performed without specific suggestions regarding the frequency, intensity, time and type (FITT) of exercise; i.e., the 'dose' of the 'medication' of the FITT principle of exercise prescription. Unfortunately, most of this area is currently unexplored and no well-designed studies have been performed for an evidence-based prescription of aerobic exercise training for vascular health among individuals with hypertension. The (limited) evidence currently available around these FITT of exercise prescription for vascular health among individuals with hypertension that determine the 'dose of exercise' is summarised below.

Frequency Studies that have examined the effects of aerobic exercise training on the vasculature have used training regimes that varied between 2 and 6 times per week [77, 87, 88, 92, 117, 188–191]. However, no direct comparisons have been made between exercise training strategies that differ in the frequency of exercise training.

Intensity Although not specifically examined in subjects with hypertension, some studies have studies the impact of different intensities of exercise upon the magnitude of vascular adaptation. A well-designed and controlled study by Goto et al. [192] examined the effects of low (25 % of maximum oxygen consumption [$\dot{V}O_{2max}$]), moderate (50 % $\dot{V}O_{2max}$), and high (75 % $\dot{V}O_{2max}$) intensity aerobic training in young men. Endothelium-dependent forearm vasodilation improved in the moderate intensity group, but not in other groups. The reason for the lack of vascular adaptation in the low intensity aerobic training group may relate to the stimulus falling below a given threshold to induce vascular remodelling. In contrast, the reason for the lack of changes in the high intensity aerobic training group is not

likely to relate to an insufficient stimulus. The authors provided evidence that increased oxidative stress may have counteracted the beneficial effects of shear stress and exercise on the vasculature among the high intensity group.

A previous study from Bergholm *et al*. provided further evidence for this hypothesis. They reported that 3 months of high intensity running in physically fit male subjects reduced endothelium-dependent function [193]. The degree of endothelial dysfunction following training was greatest in subjects with the largest improvements in $\dot{V}O_{2max}$. The authors postulated that the training-induced decrease in circulating antioxidant levels may have adversely affected endothelial function in the highly trained or overtrained state. Alternatively, one should also consider the possibility of a distinct time-course in adaptations in vascular function and structure to different intensities of exercise.

Time Although very little is known about this topic, a recent pooled analysis revealed that a larger effect of aerobic exercise training on conduit artery endothelial function can be expected after a longer training intervention [194]. Whether a comparable relation is present for resistance artery adaptations is currently unknown.

Type A more detailed comparison between aerobic and resistance exercise training will follow in Chapter 6. When comparing different types of aerobic exercise, it should be notes that more recent studies have introduced high intensity interval training (HIIT). HIIT involves repeated exposure to short periods (1–4 min) of high intensity exercise (>90 % maximal workload) interspersed with similarly long periods of low intensity exercise (<40 % maximal workload). Studies that have directly examined the impact of HIIT found improved conduit artery vasodilator function in patients with heart failure [195], the metabolic syndrome [196], and patients with coronary artery disease [197, 198]. Some studies have even directly compared HIIT with aerobic exercise training have suggested the presence of a superior effect of HIIT to improve vasodilator function [195, 196, 199], although results are conflicting [198]. While these studies highlight the presence of (potentially more) successful training interventions to alter vascular function, future studies are necessary to identify the most appropriate type of training to improve the vasculature. Please see Chapter 1 for a detailed discussion of the FITT principle of exercise prescription targeting BP among individuals with hypertension, including comment on HITT.

Conclusion

Aerobic exercise training has well-established BP lowering effects (see Chapter 1). The drop in BP is largely explained by the decline in peripheral vascular resistance, as Q does not change or even increases after training due to enlargement of the cardiac dimensions and subsequent increases in SV among healthy individuals other than their high BP. Exploring the mechanisms of the drop in BP, studies have revealed systemic improvement in vascular function as well as structural enlargement in conduit and resistance vessels. These beneficial adaptations in vascular function and structure should contribute, at least partly, to the drop in resting BP that result from aerobic exercise training among individuals with pre to established

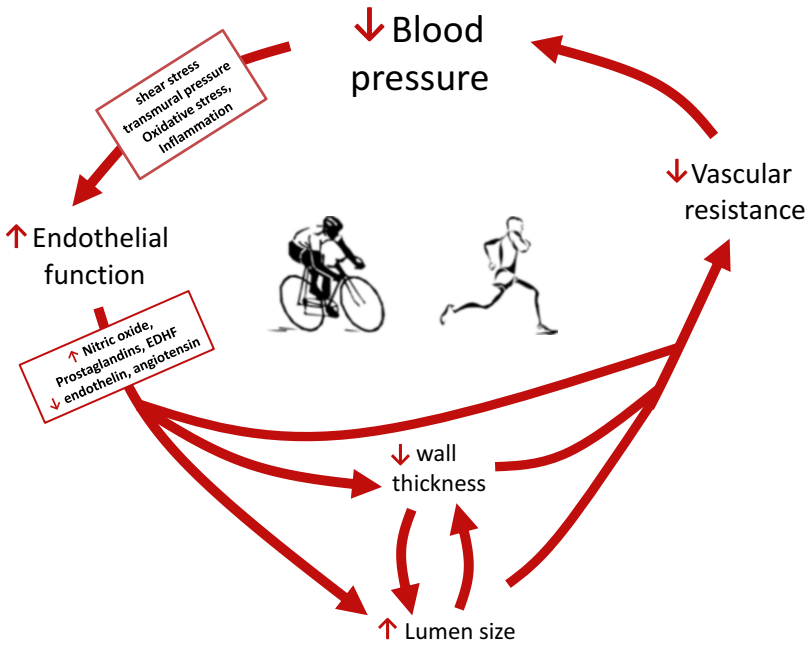

Fig. 5.3 Conceptual framework how exercise training influences blood pressure. This figure represents a conceptual framework how exercise training influences vascular function and structure, including the various hemodynamic stimuli which are presented in the boxes, ultimately leading to a decrease in peripheral vascular resistance and mean arterial blood pressure (*EDHF* endothelium-derived hyperpolarizing factor)

hypertension; while this process may also occur during the development of prehypertension and its progression to established hypertension.

Accordingly, BP appears to have a strong interplay with vascular function and structural characteristics, that both can be influenced in opposite directions (Fig. 5.3). While various stimuli such as cyclic pressure, endothelial progenitor cells and circulating hormones may contribute to the benefits of exercise, repeated increases in shear stress (or blood flow) represents a key stimulus to mediate the vascular adaptations to aerobic training. Shear stress directly acts upon the endothelium, leading to improvement in vascular function and enlargement of conduit and resistance arteries in the active and non-active regions. Such adaptations seem to bi-directionally influence BP regulation, however, the interplay among vascular adaptations as they relate to the BP reductions that occur following aerobic exercise training should be explored further to better elucidate the relationships among the two.

Key Points and Resources

- Prolonged aerobic exercise training lowers BP, especially in those with elevated levels of BP, which is likely mediated through a decrease in peripheral vascular resistance.

- Aerobic exercise training leads to (rapid) systemic improvements in vascular function, which are both evident in conduit and resistance arteries. Adaptations in vascular structure, i.e., dimension and wall thickness, occur more slowly and are predominantly present locally in physically active areas.
- In healthy subjects, the initial improvements in vascular function return towards baseline once structural enlargement of the blood vessels occur, which highlight the strong and complex interplay between functional and structural adaptations to exercise training. Whether a similar interplay is present in subjects with (pre) hypertension is currently under debate.
- Repeated elevation in shear stress, or the dragging force of blood upon the vascular wall, represents a key stimulus that mediates functional and structural vascular adaptation. Cyclic pressure and the release of circulating factors may also contribute to the benefits of aerobic exercise training on the vasculature.
- Despite the volume of literature on aerobic exercise training and vascular adaptation, there remains a critical need for randomized controlled trials in patients with hypertension to identify the FITT aerobic exercise training interventions characteristics that optimally alter vascular function and structure. This new information will eventually contribute to evidence-based prescription of optimal (and personalized) guidelines for aerobic exercise training.
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