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Vascular structure and function in physically active children and adolescents – is there a 'pediatric athlete's artery'?

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List of abbreviations

AC ..... arterial compliance
aPWV ..... aortic pulse wave velocity
aSBP ..... aortic systolic blood pressure
BMI ..... body mass index
CCA ..... common carotid artery
cfPWV ..... carotid-femoral pulse wave velocity
cSBP ..... central systolic blood pressure
DBP ..... diastolic blood pressure
ECG ..... electrocardiogram
Ep ..... elastic modulus
LDL ..... low-density lipoprotein
LV ..... left ventricle
MET ..... metabolic equivalent
MoMo-AFB ..... MoMo Physical Activity Questionnaire
MVPA ..... moderate-to-vigorous physical activity
NO ..... nitric oxide
PDPAR ..... Previous Day Physical Activity Recall
PPCS ..... pre-participating cardiovascular screening
PWV ..... pulse wave velocity
PWVβ ..... carotid pulse wave velocity
SBP ..... systolic blood pressure
VSMC ..... vascular smooth muscle cells
WHO ..... World Health Organization

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Summary

One of the most important challenges in children and adolescents is to motivate them to be physically active and exercise, as this age group develops essential habits for an active lifestyle. This is a key goal in the prevention of non-communicable diseases. The cardiovascular system responds to physical activity and exercises with long-term cardiac output improvements and heart rate reductions. This dissertation focused on how physical activity and exercise affect the vascular system in youth. The association of physical activity and exercise with vascular structure and function in exercising children and adolescents was investigated.

For this purpose, the current state of research on this topic was first summarized in a review paper. This review found favorable associations of vascular structure and function with physical activity and fitness in children and adolescents. In addition, exercise interventions have been identified as being well-suited to improve vascular morphometry in children and adolescents whose vascular properties are impaired due to underlying cardiovascular or metabolic disease. However, little evidence exists on the relationship between exercise as targeted training and vascular structure and function in children and adolescents. Therefore, the MuCAYA Study (Munich Cardiovascular Adaptation in Young Athletes Study) was designed based on these findings. One of the aims of this study was to investigate the relationship between training duration and intensity and vascular structure and function in children and adolescents.

As a result, almost 800 children and adolescents who were exercising in sports clubs were studied between 2017 and 2020. In the first analysis, only children and adolescents who met the definition of young athletes, according to Araújo and Scharhag (1), were considered. Compared with corresponding reference values of children and adolescents, young athletes showed a higher carotid intima-media thickness (cIMT) and a higher cIMT:carotid diameter ratio (cIDR). 40.8% of young athletes had cIMT > 75th percentile. Although central systolic blood pressure (cSBP) and aortic pulse wave velocity (aPWV) were significantly elevated, corresponding to increased central arterial stiffness, increased elasticity, and decreased stiffness of the common carotid artery (CCA) were evident.

Moreover, a fourth publication in this dissertation has shown the association of exercise duration and intensity with vascular properties in children and adolescents actively participating in sports clubs. Here, higher weekly training duration was associated with higher cIMT but improved carotid elasticity and lower central arterial stiffness. Higher weekly training intensity was associated with higher cIMT, carotid diameter, and carotid elasticity. Sex-specific analyses identified differences in the association of training duration and intensity with vascular properties.

In conclusion, this dissertation shows that there is a ‘pediatric athlete’s artery’, which is expressed by a higher cIMT, higher cIDR, higher elasticity, or lower stiffness of the CCA. Therefore, young athletes should be further investigated longitudinally to exclude that young athletes are at higher short- and long-term cardiovascular risk because of their increased training volume. In addition, studies, including the MuCAYA study, should examine the interplay of cardiac and vascular adaptation to exercise in physically active children and adolescents. This analysis is relevant because in this dissertation, on the one hand, the young athletes showed increased central arterial stiffness, but the population of physically active children and adolescents showed lower arterial stiffness with higher weekly training duration. The goal is to gain a better insight into the overall adaptation of the cardiovascular system to exercise in childhood and adolescence. Finally, more research is needed to determine the optimal exercise volume and intensity for different types of sports in children and adolescents to promote cardiovascular health benefits while avoiding adverse effects. This will allow the development of appropriate recommendations for physical activity and exercise in different groups of children and adolescents to promote cardiovascular health and prevent future cardiovascular disease.

Zusammenfassung

Eine der wichtigsten Herausforderungen bei Kindern und Jugendlichen besteht darin, sie zu körperlicher Aktivität und Bewegung zu motivieren, da in dieser Altersgruppe grundlegende Gewohnheiten für einen aktiven Lebensstil entwickelt werden. Dies ist ein zentrales Ziel in der Prävention von nicht übertragbaren Krankheiten. Das Herz-Kreislauf-System reagiert auf körperliche Aktivität und Bewegung mit einer langfristigen Verbesserung der Herzleistung und einer Senkung der Herzfrequenz. Im Mittelpunkt dieser Dissertation stand die Frage, wie sich körperliche Aktivität und Bewegung auf das Gefäßsystem bei Kindern und Jugendlichen auswirken. Untersucht wurde der Zusammenhang von körperlicher Aktivität und Bewegung mit der Gefäßstruktur und -funktion bei körperlich aktiven Kindern und Jugendlichen.

Zu diesem Zweck wurde zunächst der aktuelle Forschungsstand zu diesem Thema in einer Übersichtsarbeit zusammengefasst. Diese Übersichtsarbeit ergab günstige Assoziationen von Gefäßstruktur und -funktion mit körperlicher Aktivität und Fitness bei Kindern und Jugendlichen. Darüber hinaus wurde festgestellt, dass Bewegungsinterventionen gut geeignet sind, um die Gefäßmorphometrie bei Kindern und Jugendlichen zu verbessern, deren Gefäßeigenschaften aufgrund einer zugrundeliegenden kardiovaskulären oder metabolischen Erkrankung beeinträchtigt sind. Es gibt jedoch nur wenige Belege für den Zusammenhang zwischen Bewegung als gezieltes Training und der Gefäßstruktur und -funktion bei Kindern und Jugendlichen. Daher wurde die MuCAYA-Studie (Munich Cardiovascular Adaptation in Young Athletes Study) auf Grundlage dieser Erkenntnisse konzipiert. Eines der Ziele dieser Studie war es, den Zusammenhang von Trainingsdauer und Trainingsintensität mit der Gefäßstruktur und -funktion bei Kindern und Jugendlichen zu untersuchen.

Daraufhin wurden zwischen 2017 und 2020 knapp 800 Kinder und Jugendliche untersucht, die im Sportverein körperlich aktiv waren. In der ersten Auswertung wurden nur Kinder und Jugendliche betrachtet, welche die Definition für junge Athleten nach Araújo und Scharhag (1) erfüllt haben. Im Vergleich zu entsprechenden Referenzwerten von Kindern und Jugendlichen wiesen die jungen Sportler eine höhere Karotis-Intima-Media-Dicke (cIMT) und ein höheres cIMT:Karotisdurchmesser-Verhältnis (cIDR) auf. 40,8% der jungen Sportler hatten eine cIMT > 75. Perzentile. Obwohl der zentrale systolische Blutdruck (cSBP) und die aortale Pulswellengeschwindigkeit (aPWV) signifikant erhöht waren, was einer erhöhten zentralen arteriellen Steifigkeit entspricht,

war eine erhöhte Elastizität und eine geringere Steifigkeit der Arteria carotis communis (CCA) zu erkennen.

Eine vierte Veröffentlichung in dieser Dissertation hat darüber hinaus den Zusammenhang zwischen Trainingsdauer und -intensität und den Gefäßeigenschaften bei Kindern und Jugendlichen, die in Sportvereinen aktiv sind, aufgezeigt. Hier war eine höhere wöchentliche Trainingsdauer mit einer höheren cIMT, aber einer verbesserten Karotiselastizität und einer geringeren zentralen Arteriensteifigkeit verbunden. Eine höhere wöchentliche Trainingsintensität korrelierte mit einem höheren cIMT und Karotisdurchmesser, aber auch mit einer höheren Karotiselastizität. Geschlechtsspezifische Analysen ergaben Unterschiede in der Assoziation von Trainingsdauer und -intensität mit vaskulären Eigenschaften.

Zusammenfassend zeigt diese Dissertation, dass es eine „pädiatrische Athletenarterie“ gibt, die sich durch eine höhere cIMT, höhere cIDR, höhere Elastizität bzw. geringere Steifigkeit der CCA äußert. Daher sollten junge Sportlerinnen und Sportler in Längsschnittstudien weiter untersucht werden, um auszuschließen, dass junge Sportlerinnen und Sportler aufgrund ihres hohen Trainingsvolumens ein höheres kurz- und langfristiges kardiovaskuläres Risiko haben. Darüber hinaus sollten Studien, einschließlich der MuCAYA-Studie, das Zusammenspiel von kardialer und vaskulärer Anpassung an Bewegung bei körperlich aktiven Kindern und Jugendlichen untersuchen. Diese Analyse ist insofern relevant, da in dieser Dissertation einerseits die jungen Athleten eine erhöhte zentrale arterielle Steifigkeit gezeigt haben, die Gesamtheit an körperlich aktiven Kindern und Jugendlichen aber eine niedrigere arterielle Steifigkeit mit höherer wöchentlichen Trainingsdauer. Das Ziel ist, ein besseres Verständnis für die Gesamtanpassung des kardiovaskulären Systems an Bewegung im Kindes- und Jugendalter zu erhalten. Schließlich sind weitere Forschungsarbeiten erforderlich, um das optimale Trainingsvolumen und die optimale Trainingsintensität für verschiedene Sportarten bei Kindern und Jugendlichen zu bestimmen, um die kardiovaskuläre Gesundheit zu fördern und gleichzeitig negative Auswirkungen zu vermeiden. Dies wird die Entwicklung geeigneter Empfehlungen für körperliche Aktivität und Sport bei verschiedenen Gruppen von Kindern und Jugendlichen ermöglichen, um die kardiovaskuläre Gesundheit zu fördern und künftigen Herz-Kreislauf-Erkrankungen vorzubeugen.

1 Introduction

Physical activity positively affects physical and mental health during childhood and adolescence. Physical activity lowers blood pressure and improves arterial elasticity and structure (2-4). These factors reduce the risk of atherosclerosis, a thickening and stiffening of the vascular wall, and the leading cause of cardiovascular diseases (5). Children and adolescents are recommended to engage in at least 60 minutes of moderate-to-vigorous physical activity (MVPA) daily (6). However, studies that describe a positive effect of physical activity refer to moderate exercise intensities in children and adolescents (7). An active lifestyle in childhood, thus, is the cornerstone for preventing cardiovascular disease over the lifespan.

In contrast, some studies in intensively exercising adult athletes show harmful effects of physical activity on the cardiovascular system and observed physiologically altered structural and functional properties of the heart and arteries, for example, increased arterial vascular stiffness and thickened arterial walls (8, 9). The alteration of the structural and functional properties of the heart has also been described in children and adolescents. Studies indicate that especially intensively exercising adolescent athletes show physiological changes in the heart, for example, an enlargement of the left ventricle as well as the left ventricular wall thickness and an increased ejection fraction (10-12). These results are summarized under the term ‘pediatric athlete’s heart’ (13).

However, it is unclear whether the structural and functional properties of the vasculature are also altered in physically active children and adolescents and, thus, whether a ‘pediatric athlete's artery’ can be observed. Therefore, this dissertation focuses on the association of physical activity and vascular properties in exercising children and adolescents. First, a literature review will summarize and analyze the evidence regarding the association of vascular properties with physical activity, fitness, and exercise (article 1). Second, the vascular characteristics, physical activity, and performance of children and adolescents who are active in sports clubs are investigated (article 2). Out of these children and adolescents, those who meet the definition of young athletes, according to Araújo and Scharhag (1), will be identified. The vascular properties of these young athletes are compared with the vascular properties of reference collectives to determine possible vascular adaptations to exercise (article 3). Conclusively, the relationship between vascular properties and training-specific parameters (duration, intensity) is analyzed with all children and adolescents who are active in sports clubs (article 4).

1.1 Physical activity, exercise, and physical fitness

Physical activity, exercise, and physical fitness are all terms used in the context of human movement behavior. Since the terms describe different approaches but are often misused, they will first be defined.

Physical activity is *“any bodily movement produced by skeletal muscles that requires energy expenditure. The amount of energy required to accomplish an activity can be measured in kilojoules (kJ) or kilocalories (kcal)” […] Expressed as a rate (kcal per unit time), the amount of energy expended by each person is a continuous variable, ranging from low to high”* (14). Physical activity can be structured (e.g., exercise) or incidental due to daily activities (15).

Thus, exercise is a subcategory of physical activity. Exercise is also a bodily movement via skeletal muscles that results in energy expenditure ranging from low to high. Moreover, exercise *“is planned, structured, repetitive, and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective”* (14).

Physical fitness refers to health-related physical fitness and skill-related physical fitness. Physical fitness is not defined as a body movement but as a set of attributes necessary to perform physical activity. Health-related physical fitness comprises cardiovascular endurance, muscular endurance, muscular strength, body composition, and flexibility. The skill-related physical fitness combines the motor components of agility, balance, coordination, speed, power, and reaction time. Both physical activity and exercise result in energy expenditure and are positively associated with physical fitness (14).

Physical activity occurs in the following four domains occupational (e.g., carrying objects), domestic (e.g., housework), transportation/utilitarian (e.g., climbing/descending stairs to public transportation), and leisure time (e.g., hobbies) (15). In addition to the domains of physical activity, the dimensions of physical activity are also essential to understand the construct of physical activity. Strath et al. (15) describe four dimensions of physical activity, which are explained in Table 1:

Table 1. Definition and context of the four dimensions of physical activity (15)

Dimension	Definition and context
Mode	Specific activity performed (e.g., walking, gardening, cycling)
Frequency	Number of sessions per day or week
Duration	Time (minutes or hours) of the activity bout during a specified time frame (e.g., day, week, year, past month)
Intensity	Rate of energy expenditure

As physical activity leads to energy consumption, the intensity commonly indicates the energy expended while being physically active. The metabolic equivalent (MET) is the parameter used to quantify energy consumption. It is defined as the ratio of the metabolic rate during work to the metabolic rate at rest. One MET corresponds to 1.0 kcal/kg body mass/h or 3.5 ml/kg body weight/min. In general, the types of physical activity can be classified as sedentary behavior (1.0 – 1.5 METs) and light-intensity (1.6 – < 3.0 METs, e.g., walking slowly, household activities, billiard), moderate-intensity (3.0 – < 6.0 METs, e.g., light cycling, golf, dancing), and vigorous-intensity (≥ 6.0 METs, e.g., jogging, soccer, basketball) activities. (16). The Compendium of Physical Activities of Ainsworth et al. (16) allows one to assign a MET value to any physical activity and thus to record intensity precisely. Since energy costs in relation to body weight decrease with increasing age, the MET values of adults cannot easily be transferred to those of children and adolescents (17). Thus, a Compendium of Energy Expenditures for Youth has been developed by Ridley et al. (18).

An active lifestyle starts to develop in childhood and adolescence. Those who integrate physical activity into their daily lives as children or adolescents are more likely to be physically active as adults and thus benefit from the positive effects on their health (19, 20). The World Health Organization (WHO) recommends that children and adolescents aged between 5 and 17 years should engage in MVPA at least 60 minutes per day. These activities should mostly be aerobic. Furthermore, children and adolescents should engage in vigorous-intensity aerobic activities and activities that strengthen muscle bones at least three days per week (6). In addition to the WHO recommendations, Germany has recommendations on the amount of physical activity for children and adolescents. Graf et al. (21) recommend a daily physical activity of at least 90 minutes or 12,000 steps.

The overall activity level of German boys and girls is needs to be increased: only 22.4% of girls and 29.4% of boys currently meet the WHO recommendation of at least 60 minutes of MVPA per day. With increasing age, however, the number of children and adolescents who fulfill the WHO recommendation decreases. Among the 3-to-6-year-olds, 42.5% (girls) and 48.9% (boys) meet the WHO recommendation. Then, however, the proportion drops rapidly so that in the 11- to 13-year-old age group, only 16.5% (girls) and 21.4% (boys) meet the WHO recommendation, and in the 14- to the 17-year-old age group, it is only 7.5% in girls and 16.0% in boys (22). In the Health Behavior in School-Aged Children (HBSC) Study, which compares the physical activity of children and adolescents from 44 countries, Germany ranks only in the lower third. On average, 25% of the 11-year-olds (21% girls, 30% boys), 20% of the 13-year-olds (15% girls, 25% boys), and 16% of the 15-year-olds (11% girls, 21% boys) reported at least 60 minutes in MVPA per day. Worldwide, the proportion of 11- to 17-year-olds who do not engage in moderate to intensive physical activity for at least 60 minutes a day is 81.0% in total, 77.6% in boys, and 84.7% in girls. There is a trend that the prevalence of those who do not meet the WHO recommendation has decreased by 2.5% in boys between 2001 and 2016 but not in girls (23). In addition to age and sex, other factors associated with reduced exercise behavior in children and adolescents are overweight and obesity (24), elevated blood pressure and cardiometabolic parameters (25, 26), lower socioeconomic status (27), migration background (28), very high media use (29), and reduced parental physical activity (30).

There are many options for quantifying physical activity, which can be divided into two types of methodology: subjective and objective methods (see Table 2). Each method has its strengths and limitations, and due to the enormous variety, the choice of method can be challenging. Which method of assessing physical activity is used depends on the requirements of each study, e.g., outcome variable, number and age of study subjects, financial budget, staff resources, and target parameter. In extensive studies with many participants, physical activity questionnaires are often used. The advantage of questionnaires is, for example, that many persons can be measured without high costs, different dimensions of physical activity can be collected, and energy expenditure can be calculated. On the other hand, there is the disadvantage that there can be difficulties in memorize exercise behavior, especially with children and adolescents. Furthermore, some terms can be unclear for the respondents, and some questionnaires are not filled out completely (31).

Table 2. Subjective and objective methods of measuring physical activity (15)

Subjective	**Objective**
Physical activity questionnaires • Global physical activity Questionnaires • Short recall physical activity questionnaires • Quantitative history physical activity questionnaires	Measures of energy expenditure • Indirect calorimetry • Doubly labeled water method • Direct observation
Physical activity diaries/logs	Physiological measures: Heart rate monitoring
	Motion sensors: • Accelerometers • Pedometers
	Multisensing assessment methods

1.2 Anatomy and physiology of blood vessels

Starting from the heart, blood is pumped through arteries into circulation. First, oxygen-rich blood flows through elastic arteries close to the heart (aorta, carotid artery) and peripheral muscular arteries (femoral artery). Through arterioles, the blood flows into capillaries, where gas is exchanged. Subsequently, oxygen-poor blood is transported back to the heart in venules and veins.

The arterial wall is composed of three layers, the intima, media, and externa or adventitia (see Figure 1). The tunica intima is the inner layer of the vessel wall and consists of a single layer of endothelial cells and a subendothelial layer of connective tissue. The tunica media is the middle layer of the vessel wall and is composed of circularly arranged vascular smooth muscle cells (VSMC) with the extracellular matrix. The tunica externa or adventitia is the outer layer of the vessel wall and consists of perivascular adipose tissue cells, fibroblast cells, collagen fibers, and nerve endings. Tunica intima and media are separated by the internal elastic membrane, tunica media and adventitia by the external elastic membrane (32, 33).

The single layer of endothelial cells is located directly at the vessel's lumen. Therefore, it can detect blood-transmitted signals and react to changes in blood flow and composition (34, 35). Essential functions of endothelial cells are the provision of a semipermeable barrier between the vessel lumen, regulation of the vascular tone by releasing vasoactive substances, modulation of cell adhesion and inflammation of the vascular system, modulation of hemostasis and coagulation and angiogenesis (32).

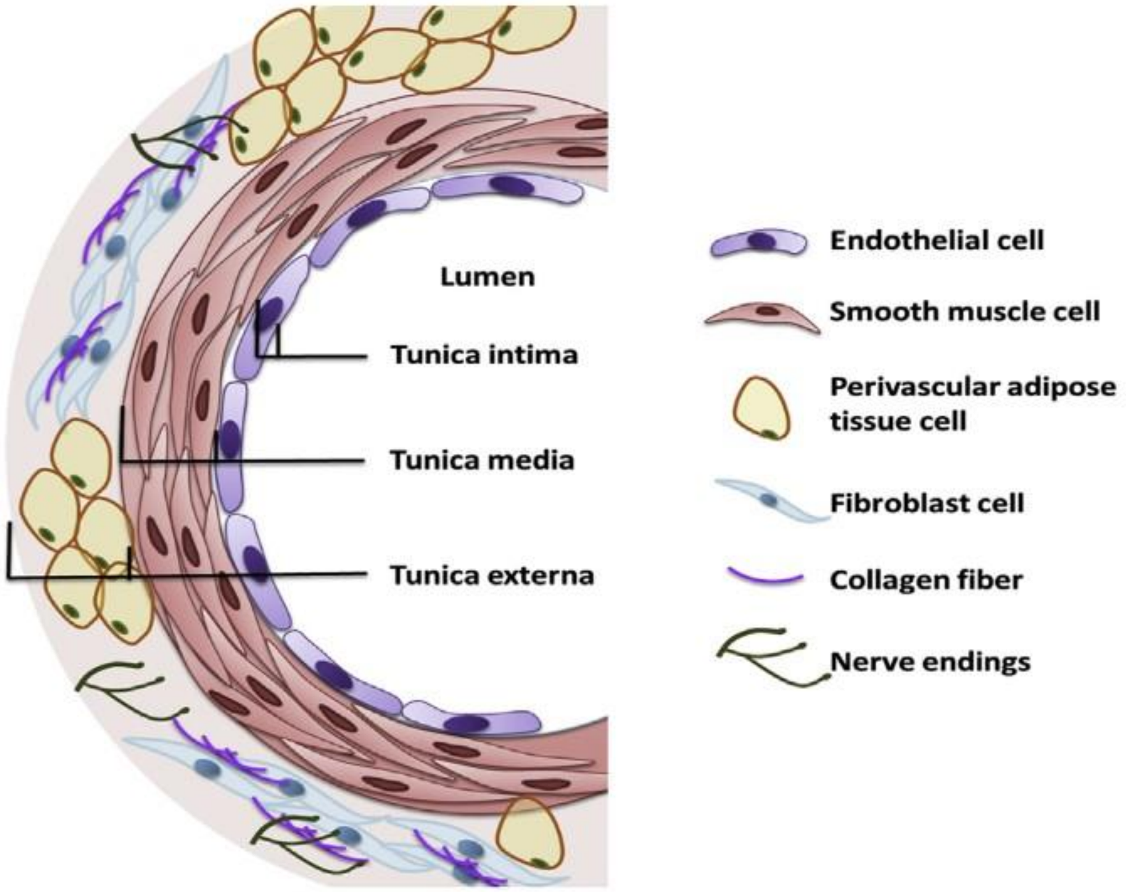

Figure 1: Structure of the arterial wall (33)

The most prominent cell types of arteries are VSMC localized in the medial layer (32). They are essential for arterial contraction and have an important role in compliance and elastic recoil of the artery in response to altered hemodynamic conditions (36). VSMC play a significant role in the pathogenesis of vascular diseases like atherosclerosis and hypertension (36, 37). While elastic arteries have higher levels of elastin and important pulse-smoothing properties to conduct the pressure wave generated in the left ventricle, muscle arteries have a higher level of smooth muscle cells in relation to elastin. They distribute the blood according to the current demand and are more capable to constrict and dilate the vessels (38).

Blood pressure regulation is one of the most important functional roles of the vascular system. Blood is pumped through the vascular system into the circulatory system with every heartbeat, exerting pressure on the walls of the blood vessels. Here, the contractile phase (systole) and the resting phase (diastole) are distinguished. Systolic blood pressure (SBP) is the pressure that occurs when the heart muscle contracts and pumps blood to the periphery. Diastolic blood pressure (DBP) is the pressure during the filling phase of the ventricles. The difference between the maximum value (SBP) and the minimum value (DBP) is the pulse pressure (39).

In particular, the arterial system has two hemodynamic functions. The conduit function describes the artery behaving like a tube to provide adequate blood supply from the heart to the periphery. The second function of arteries is to dampen the pressure fluctuations and to provide a nearly constant flow of the peripheral tissues and organs (40). These abilities of arteries are described with arterial compliance (AC), distensibility, or stiffness. The distensibility is the relative change in volume per unit pressure (41). Compliance is defined as the ratio volume change pressure change. Stiffness means the opposite of compliance. Whereas at low strain pressure, the tension is supported by elastic fibers, at high strain pressure, the tension is transferred to and supported by less stretchable collagen fibers. This leads to a stiffer artery wall. Since stiffness increases with higher blood pressure, arterial stiffness is always related to the present pressure (40). Stiff arteries have a decreased capacity for arterial dilation and recoil in response to pressure changes (42).

An essential characteristic of elastic arteries is the Windkessel function. It describes how elastic arteries can convert the pulsating blood ejections from the heart into a steady blood flow. Elastic arteries expand passively due to the blood pressure and temporarily store parts of the blood volume. During diastole, elastic arteries retract, pushing the accumulated blood volume along the arterial tree (43). The pressure wave created when blood is ejected from the left ventricle spreads through the arterial tree and is reflected when it encounters sites of unequal impedance, such as at a bifurcation (44, 45). The pulse wave velocity (PWV) is the speed at which the arterial pulse wave travels along the arterial wall (46). The augmentation pressure describes the extent to which the reflected wave still falls into the systolic phase and thus increases pressure. The stiffer the vessel, the earlier the reflected wave falls into the systolic phase and the higher the augmentation pressure. The proportion of the augmentation pressure to the pulse pressure is described as the augmentation index (47). Because the stiffness of the arteries increases from central to peripheral, the pressure curves change, and the augmentation pressure and, thus, the augmentation index increase (44).

1.3 Assessment of vascular function and wall thickness

Blood pressure is usually measured at the brachial artery but is less predictive of cardiovascular risk than aortic blood pressure (48). Since central blood pressure varies with age, sex, height, and heart rate, and brachial pressure does not predict central pressure sufficiently, central pressure must be assessed with suitable measurement methods (44). The central SBP (cSBP) can be measured using devices that work with applanation tonometry (e.g., SphygmoCor) or oscillometry (e.g., Mobil-O-Graph®, Arteriograph). Besides, the oscillometric devices differ in the method of waveform recording: brachial cuff pulse volume plethysmography (Mobil-O-Graph®) or supra systolic brachial cuff pulse volume plethysmography (Arteriograph). Depending on the device, the central pressure can be estimated by measuring the pressure on various arteries (49).

The gold standard of arterial stiffness measurement is carotid-femoral PWV (cfPWV) (50). In this measurement, the transit time of signals between the carotid and femoral arteries is measured and used to derive the aortic PWV (aPWV) (46). The peripheral arterial waveforms can be recorded tonometrically (tonometry of the radial and femoral arteries) or cuff-based (cuff on the brachial and femoral arteries) (51). Other methods of assessing aPWV via transit time are a cuff-based measurement of brachial-ankle PWV, photo-plethysmographic devices on fingers and toes, or the cardio-ankle index (46).

Furthermore, waveform analysis can indirectly estimate the aPWV with underlying algorithms. A cuff-based measurement is performed on the brachial artery. The Arteriograph and Mobil-O-Graph® are examples of this method of PWV measurement (46). Arterial stiffness can also be measured with ultrasound locally at the respective artery. The measurement at the common carotid artery (CCA) is particularly relevant here, as the risk of arteriosclerosis can be derived from this artery. The measurement of arterial stiffness is based on the change in diameter to the local blood pressure (47). Local vascular stiffness can also be measured by magnetic resonance imaging. However, this type of measurement is rarely performed due to higher costs and ethical reasons (46).

Since the heart, kidneys, and main arteries supplying the brain are more exposed to aortic pressure than brachial pressure, cardiovascular events are more likely associated with central than brachial pressure (44). Both central hemodynamics (cSBP and aPWV) and arterial stiffness parameters are important indicators of vascular health. They are related to age, sex, body mass index (BMI), cIMT, cardiovascular events, cardiovascular mortality, and all-cause mortality (44, 52-55). Furthermore, central hemodynamics and arterial stiffness parameters are related to health behaviors like smoking and diet (56, 57). Besides, higher levels of physical activity and physical fitness are associated with better central hemodynamics across the lifespan (58-60).

The most meaningful parameter for the arterial structure is the intima-media thickness measurement. The cIMT has been established as a subclinical parameter for assessing the vascular structure and estimating cardiovascular risk (61). The cIMT is measured at the CCA and in a longitudinal and cross-sectional view via B-mode ultrasound. The cIMT is determined in the transversal scan on the far wall over the area of 1 cm before the bifurcation of the CCA into the internal and external CCA (62). Another parameter is the vessel lumen or diameter measured at the same location as the cIMT. Out of these two parameters, the ratio of cIMT and carotid lumen or diameter can be calculated (63).

In addition to the cIMT as an essential surrogate parameter for atherosclerosis, cIMT is a noninvasive biomarker for assessing cardiovascular risk (63, 64). An increased cIMT is associated with a higher risk of myocardial infarction, stroke, cardiovascular disease, and cardiovascular disease-related death in adults (65). BMI, mean arterial pressure, heart rate, and cIMT are predictors of carotid lumen diameter (66). Furthermore, associations between cIMT and BMI, fat-free mass, blood pressure, low-density lipoprotein (LDL), metabolic syndrome, and cardiovascular risk score are already evident in childhood and adolescence (67-70).

1.4 Physical activity and exercise effects on vascular properties

1.4.1. Biochemical principles of vascular adaptation

The biochemical process of vascular adaptation to physical activity is very complex and is explained extensively in the article by Green et al. (71). A variety of biochemical messengers in the endothelium and smooth muscle cells are involved in vascular adaptation. The initial stimulus is mechanical, triggered by increased pressure on the vessel wall or the transmission of shear stress (see Figure 2).

Exercise leads to an increase in heart rate and SBP, which induces the aorta to stretch and causes the growth rate of endothelial cells to increase. Due to the ability of the arteries to yield to the increased pressure, this also leads to circumferential stress and, due to the pulsatile nature of the arterial blood pressure, to cyclic circumferential strain. Subsequently, mechanical stimuli activate various chemical signaling systems in the endothelium, resulting in numerous intracellular signaling cascades. The cyclic circumferential strain can also be induced by the relaxation of VSMC, which induces vasodilation and stretching of the endothelial layer. Gene expression of vascular cells may also be modified by increased cyclic circumferential stress. The exercise-induced increase in cyclic circumferential stress increases the endothelial nitric oxide (NO) synthase expression, the release of reactive oxygen species, and the expression of adhesion molecules. This also increases NO production. Furthermore, NO induces activated potassium channels stimulated by calcium, which leads to hyperpolarization and dilation of VSMC (71).

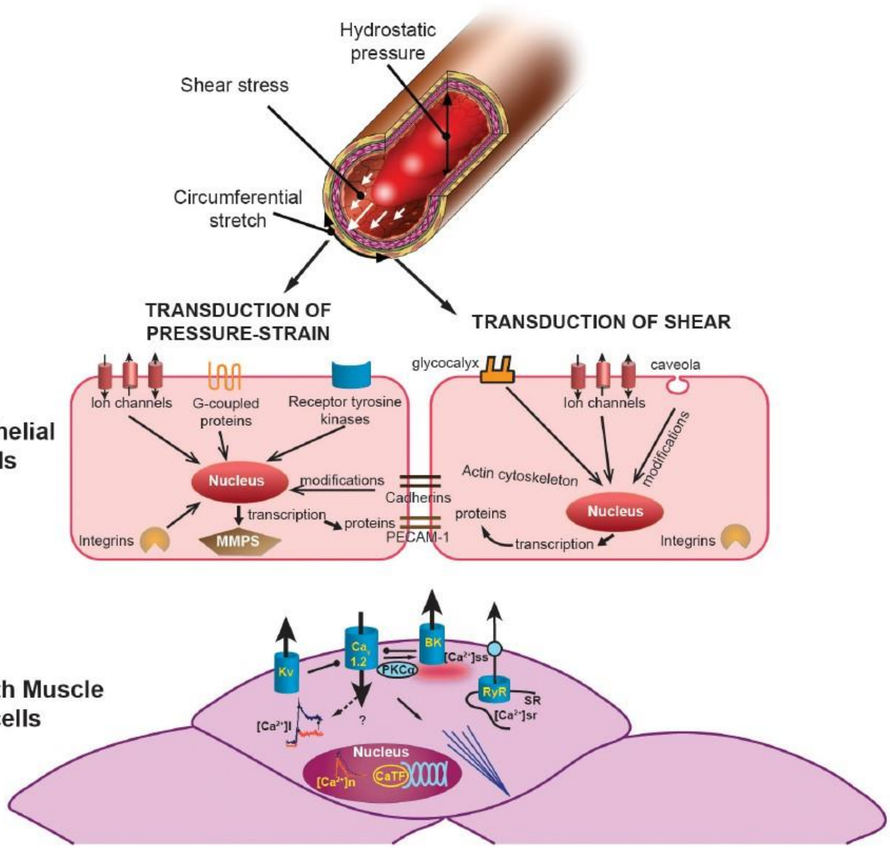

Figure 2. Exercise-induced adaptation of smooths muscle cells (bottom), effects of stretch and/or pressure on endothelial cells (middle), and interactions of hemodynamic stimuli that modulate vascular adaptation to exercise (top) (71)

Endothelial shear stress also plays an essential role in vascular adaptation to exercise. Ion channels and cell membrane receptors, among others, detect shear stress at the endothelium and thus initiate mechanotransduction, which then increases the production of shear-stress-induced NO (71). According to Rodbard (72), the exercise-induced increase in shear stress leads to an increase in flow and drag, resulting in acute dilatation during drag and, thus, functional change. Chronic exposure to exercise and chronic increase in flow and shear can remodel the vessel by structurally dilating the lumen and restoring the local resistance to its initial value.

In addition to the enlargement of the lumen, exercise can also lead to a structural change in the arterial wall. However, shear forces alone are not responsible for a reduction in wall thickness. The vascular tone plays an important role. According to Thijssen et al. (73), an exercise-induced reduction of vascular tone leads to a structural decline of the wall thickness.

1.4.2. Vascular health benefits of physical activity and exercise

Physical activity is essential for physical and mental health at any age. Physical activity reduces the rates of all-cause mortality, cardiovascular and metabolic diseases, cancer, depression, and falls (74-76). Besides, long-term studies show that the risk of mortality in the life span can be reduced by increasing physical activity, even if people were previously inactive (77). Randomized controlled trials with different types of exercise as intervention also demonstrate an improvement in health status and a reduction in mortality risk and non-communicable diseases (78, 79). Exercise, therefore, plays an essential role in health promotion and primary, secondary, and tertiary prevention.

Physical activity and exercise have several vascular health benefits. Physically active individuals are more likely to have lower blood pressure levels and are at lower risk for hypertension. Targeted aerobic exercise interventions with moderate to high intensities in patients with hypertension effectively lower elevated blood pressure levels (80). The cSBP and PWV are lower in physically active individuals, and targeted exercise interventions can reduce high values (81-84). Furthermore, physical activity is associated with lower arterial stiffness and increased AC (85, 86). In addition, exercise enhances vasodilator function and improves AC (87). A meta-analysis of randomized controlled trials investigating the effect of exercise modalities on vascular function revealed a significant reduction in PWV and augmentation index in aerobic exercise trials. The decrease in PWV was most effective in patients with stiffer arteries and an exercise duration of more than ten weeks. Moreover, the augmentation index improved with higher intensity of training sessions rather than with a weekly duration of training (88).

Physical activity and exercise also affect vascular structure (see Figure 3). Exercise training is associated with enlargement of the luminal diameter and reduced wall thickness. In contrast, exposure to cardiovascular risk factors is associated with a reduction of luminal diameter and an increase in wall thickness (89).

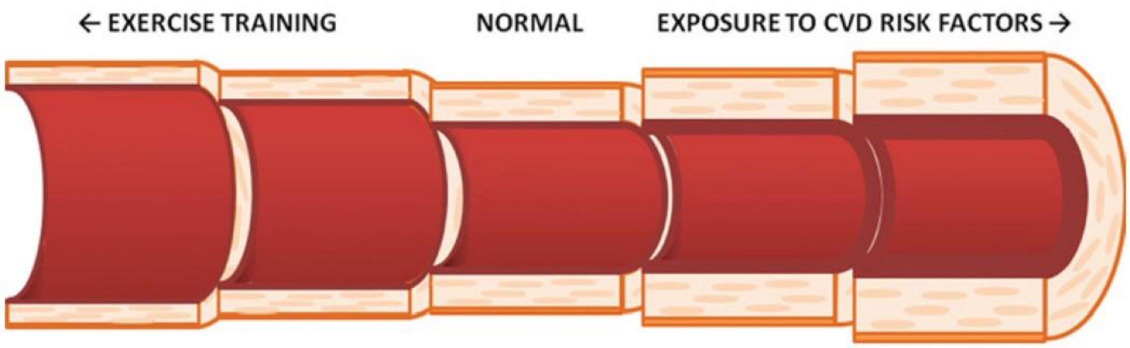

Figure 3. Impact of exercise training and exposure to cardiovascular risk factors on wall thickness and luminal diameter (89)

Even in children and adolescents, physical activity and exercise positively affect vascular health. In healthy populations, exercise reduces peripheral and cSBP and aPWV in children (90). In pediatric populations at risk, such as overweight and obese children and adolescents, aerobic and combined aerobic and strength exercise reduce BMI, fat mass, and body fat and improve flow-mediated dilation (91, 92). Furthermore, exercise interventions can reduce cIMT in obese children and adolescents (93). What impact cardiovascular risk factors in childhood can have, was shown by Raitakari et al. (94): cIMT in adulthood was significantly associated with childhood LDL, SBP, BMI, and smoking. Therefore, promoting a healthy lifestyle in childhood and adolescence is very important.

1.4.3. Vascular adaptation to exercise in athletes

While the concept of the 'athlete's heart' describes the adaptation of the heart to chronically high training loads, the analogous concept also exists for the vascular system, the 'athlete's artery' (95). The 'athlete's artery' is characterized by the remodeling of arterial size and arterial wall (see Figure 4).

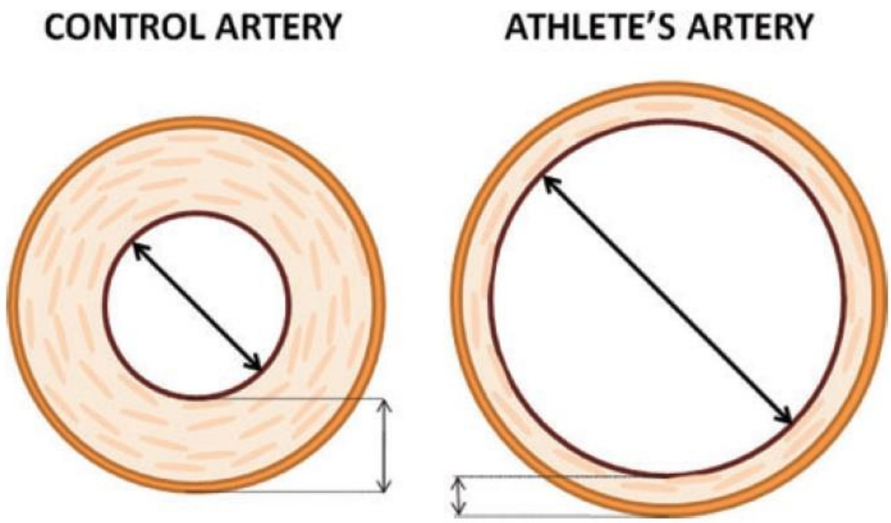

Figure 4. Representation of the 'athlete's artery', characterized by an enlarged lumen diameter and reduced wall thickness compared to controls (95)

Lumen diameter

Athletes were shown to have increased lumen diameter of brachial and femoral arteries, which has been observed in both resistance and endurance athletes compared to control subjects (96). Results for an enlargement of the aorta and carotid arteries are less consistent (95). However, the extent of the diameter adaptation seems limited to those vessels supplying the physically active limbs (71). Huonker et al. (97) examined the lumen diameter of the aortic arch, abdominal aorta subclavian artery, and common femoral artery in tennis players, cyclists, and controls. They observed a larger diameter of the subclavian artery in the racket arm of tennis players compared to the opposite arm and a larger diameter of the femoral artery in cyclists compared to untrained controls.

Besides, Rowley et al. (98) found a larger diameter of the brachial artery in upper-limb athletes but not in lower-limb athletes compared to controls. Furthermore, they observed a larger diameter of the superficial artery in both upper and lower-limb athletes compared to controls. In contrast, no difference in carotid diameter between athletes and controls was observed. Hafner et al. (8) also could not detect any differences in the diameter of the CCA. Still, they found a larger diameter of the brachial and popliteal artery in marathon runners compared to controls. In contrast, resistance athletes showed larger aortic root diameters measured at the annulus, sinuses of Valsalva, sinotubular junction, and ascending aorta (99). In addition, D'Andrea et al. (100) observed larger aortic root diameter, measured at the aortic annulus, sinuses of Valsalva, supra-aortic ridge, and ascending aorta, in strength athletes compared to endurance athletes and controls.

Black et al. (101) concluded in their meta-analysis that the exercise mode significantly impacts the arterial diameter. At the same time, endurance athletes have a larger brachial artery diameter, mixed athletes have a larger femoral and carotid artery diameter, and resistance athletes have a larger aortic diameter than controls.

Wall Thickness

The arterial wall diameter also adapts to chronic exercise and is reduced in athletes compared to controls. Results from cross-sectional studies that have compared athletes with a control group indicate that endurance training is associated with a systemic effect on wall thickness (98). Several studies observed lower cIMT in athletes compared to controls (102-105). Furthermore, Rowley et al. (98) investigated the wall thickness of the carotid, brachial, and superficial artery. They found lower wall thickness in all examined arteries in athletes (canoers, runners, and cyclists) compared to controls. In contrast, Bjarnegård et al. (106) and Sotiriou et al. (107) did not observe differences in cIMT between young female endurance athletes and dynamic and static athletes and controls, respectively. However, some studies have observed higher IMT in strength athletes, summarized by Böhm and Oberhoffer (108) in their brief report (109, 110). Also, Agrotou et al. (105) found higher cIMT in weightlifters compared to tennis players and controls. Therefore, the adaptation of the arterial wall seems to depend on the type of sport. While most of the studies with endurance athletes show a reduced wall thickness, the wall thickness may be increased in resistance athletes (111).

Wall-to-lumen/diameter-ratio

Compared with arterial lumen diameter and wall thickness, the ratio of wall thickness to lumen diameter has rarely been studied. This parameter is essential because it indicates the proportion of the arterial wall to the arterial lumen or diameter. Regarding the ‘athlete’s artery’, a lower wall-to-diameter ratio is evident in athletes, as the wall thickness is thinner and the diameter is larger compared to controls. This was also the conclusion of Rowley et al. (98). Canoers, runners, and cyclists showed significantly reduced wall-to-lumen ratio of the carotid, brachial, and superficial artery wall-to-lumen ratio compared to controls. Marathon runners had reduced total wall thickness to lumen ratio of the brachial artery but not the carotid and popliteal artery (8).

Vascular function

Although physical activity and exercise lead to improved vascular function, Green et al. (95) paradoxically suggested that vascular function is not improved in athletes compared with controls. They explain the normal vascular function in athletes by the fact that vascular function, briefly enhanced by exercise, is displaced by structural remodeling of the artery as increased shear stress returns a vascular function to normal. However, this conclusion mainly refers to the function of the endothelium measured via flow-mediated dilation. Regarding the vascular function of conduit arteries, a slightly different result emerges. Studies observed lower stiffness index β (112, 113) in endurance athletes but higher stiffness index β (114) and elastic modulus (Ep) (114) in strength athletes. Moreover, the distensibility and AC are higher in endurance athletes (112, 113, 115) but lower in strength athletes (100, 116). In summary, endurance athletes seem to have lower arterial stiffness and better AC or distensibility. In comparison, strength athletes seem more likely to have higher arterial stiffness and lower AC or distensibility.

Central hemodynamics

The effect of exercise on central hemodynamic parameters between endurance and strength sports is inconsistently evident. Studies observed lower carotid-radial PWV (106), cfPWV (112, 117), and aPWV (116) in endurance athletes. In contrast, Vlachopoulos et al. (9) found higher cfPWV and aortic SBP (aSBP) in marathon runners than in controls. Also, Laurent et al. (117) observed higher carotid SBP in endurance athletes than in controls, and Bjarnegård et al. (106) observed higher cSBP in female whole-body endurance athletes than in female runners. In strength athletes, studies observed higher aPWV (116, 118), femoral-dorsalis pedis PWV (114), aortic stiffness (100), and higher cSBP (114). In contrast, lower aSBP was observed in handball players compared to controls (119). Besides, no differences were observed between dynamic and static athletes and controls (107), between long-term trained male basketball athletes and matched controls (120), and between competitive endurance athletes and recreational athletes (121). A study by Tomschi et al. (118) compared adult elite athletes with age-matched healthy controls and found no differences in cSBP.

Influencing factors

There are some factors influencing the adaptation to exercise (71). First, adaptation tends to occur at the vessels closest to the limbs being trained (e.g., the subclavian artery in tennis players, the femoral artery in rowers). On the other hand, the type of training also plays a role. While both endurance and strength exercise are associated with increased lumen diameter, endurance exercise correlates with improved vascular elasticity, and resistance training correlates with increased arterial vascular stiffness. Furthermore, the duration and intensity of exercise are independent determinants of vascular properties and play a significant role in adaptation to exercise (9, 100). Goto et al. (122) found the most important beneficial effects of moderate-intensity training compared with mild- and high-intensity training. According to the authors, there is a dose-response relationship whereby high-intensity training flattens the beneficial impact due to higher oxidative stress and inflammation. The study by Arnold et al. (85) even observed stiffer arteries during intense physical activity, thus an inversion of the actual favorable effect of physical activity. Furthermore, the interaction of structural and functional vascular adaptations seems time-dependent. Laughlin (123) concluded that the vessel responds to acute exercise with improved vascular function due to the enhancement of vascular dilator function to normalize shear stress. Continued activity leads to subsequent vascular structural remodeling, a permanent normalization of shear stress, and adaptation of vascular function to baseline (71).

Evidence in young athletes

Unlike all the studies mentioned above referred to adulthood, there are only a few results for exercising children and adolescents. However, the evidence is unclear or, due to the small number of studies, not yet meaningful. Rátgéber et al. (124) observed no differences in aPWV between adolescent basketball players and age-matched healthy volunteers. Demirel et al. (125) examined the vascular properties in young male wrestlers and age- and sex-matched controls. They observed a higher cIMT in young wrestlers than in controls but no differences in compliance, distensibility, and elastic modulus. Studies in pediatric collectives focus less on the differences between young athletes and non-athletes and more on the relationships between vascular properties and physical activity or physical fitness in youth (126-128).

Summary

The concept of the ‘athlete's artery’ refers to the adaptation of the arterial system to chronic exercise. Athletes have larger arterial lumen diameter, thinner arterial wall thickness, and a lower wall-to-diameter ratio, with the magnitude of the adaptation depending on the type of sport, duration, and intensity of exercise. Endurance athletes generally display better arterial distensibility, lower arterial stiffness, and better central hemodynamic parameters than strength athletes. However, the evidence for children and adolescents needs to be clarified.

1.5 Aim of the dissertation

Given the studies mentioned above on the effects of exercise on the cardiovascular system, the question arises whether these effects can already be observed in childhood and adolescence and whether there is a 'pediatric athlete's artery'. To answer these research questions in this dissertation, four scientific articles were published with the following objectives:

- Give an overview of the current literature on exercise and vascular properties in childhood and adolescence.
- Assess vascular properties in exercising active children and adolescents.
- Compare vascular properties with age- and sex-specific reference values.
- Investigate the influence of the exercise stimuli duration and intensity on vascular properties.

2 Methodology

2.1 Study design and participants

This dissertation focuses on children and adolescents aged 7 to 18 who have completed a pre-participating cardiovascular screening (PPCS). The data basis for this dissertation was the MuCAYA study and the initial pilot study. The data was collected between November 09th, 2017, and September 11th, 2020, at the sports medical outpatient department for children and adolescents at the Institute of Preventive Pediatrics at the Technical University of Munich. Sports aptitude tests and examinations for cardiovascular, metabolic, or oncological diseases are conducted in this outpatient department. The children and adolescents visited the outpatient department because either the sports club, sports association, or school required a certificate of sports aptitude or they were interested in receiving a certificate of their state of health and physical performance.

During the investigation, 796 children and adolescents visited our sports medicine outpatient department, 58 with underlying diseases. Twenty-seven subjects were either under seven years or older than 18 years. Given that several sports clubs and associations require an annual statement on the sports aptitude of their athletes, 141 children and adolescents were examined twice, 33 three times, and 4 four times during the examination period. Only the first of multiple investigations for this dissertation was included in the analysis. Therefore, the final data set comprised 534 active children and adolescents.

All children and adolescents or their legal guardians were informed and asked in advance if they would like to participate in the study-relevant investigations and gave written informed consent to participate in the study. The Ethics Committee of the Technical University of Munich approved the study (project numbers 301/18 S and 131/19 S-SR).

2.2 Research methods

2.2.1. Blood pressure and central hemodynamics

Brachial SBP and DBP, cSBP, and aPWV were obtained with a single measurement using the automated oscillometric device Mobil-o-Graph® (IEM, Stolberg, Germany). Before the measurement, the subjects were in a supine position for 10 minutes. An upper arm cuff was applied to the left arm depending on the circumference of the upper arm

(XS: 14 - 20 cm, S: 20 - 24 cm, M: 24 - 32 cm, L: 32 - 38 cm, XL: 38 - 55 cm). The Mobil-O-Graph® is a validated instrument for measuring blood pressure and central hemodynamics (129-131). cSBP and aPWV were calculated indirectly from pulse waves assessed at the brachial artery using the ARCSolver Algorithm (Austrian Institute of Technology, Vienna, Austria) (132). The estimated aPWV of the Mobil-o-Graph® showed very good accuracy with invasive measured PWV (133). Using the reference values of Neuhauser et al. (134) for brachial blood pressure and Elmenhorst et al. (135) for cSBP and aPWV, standard deviation scores were assigned to the raw values.

2.2.2. Carotid structure and function

Carotid structure and function were assessed by semi-automated ultrasound with a high-frequency linear array probe of 5-13 MHz (ProSound Alpha 7; Aloka/ Hitachi Medical Systems GmbH, Wiesbaden, Germany). The cIMT, carotid diameter, and cIDR were measured as parameters for carotid structure, AC as a parameter for carotid elasticity, and β stiffness index, Ep, and carotid PWV (PWVβ) as parameters for carotid stiffness. All children and adolescents were examined in a supine position after 15 minutes of rest. The head was slightly extended, and the head turned 45° to the opposite side.

cIMT was examined in B-Mode according to the recommendation of the Association for European Paediatric Cardiology Working Group on Cardiovascular Prevention (136). A total of 4 measurements were performed at different angles, two on the right (120° and 150°) and two on the left side (210° and 240°). The Meijer’s Carotid Arc® was used for the exact positioning of the transducer for standardized measurement of cIMT at the four angles (137). The measurement point was at all angles at the far wall 1 cm before bifurcation during the end-diastolic phase. First, the bifurcation at the CCA was identified in the transverse scan, and then in the longitudinal scan, the CCA was placed in the center of the image so that the near and far walls were visible. Several cardiac cycles were recorded with the parallel three-lead electrocardiogram (ECG). After completion of the recording, the end-diastolic phase was identified referring to the ECG’s R-wave, and the image with the highest quality was selected. The cIMT measurement of the ProSound Alpha 7 is semi-automatic, which means that first, the 1 cm area to be measured was determined. Then the ultrasound software automatically defined the boundaries between lumen-intima and media-adventitia, which the examiner could manually adjust (see Figure 5).

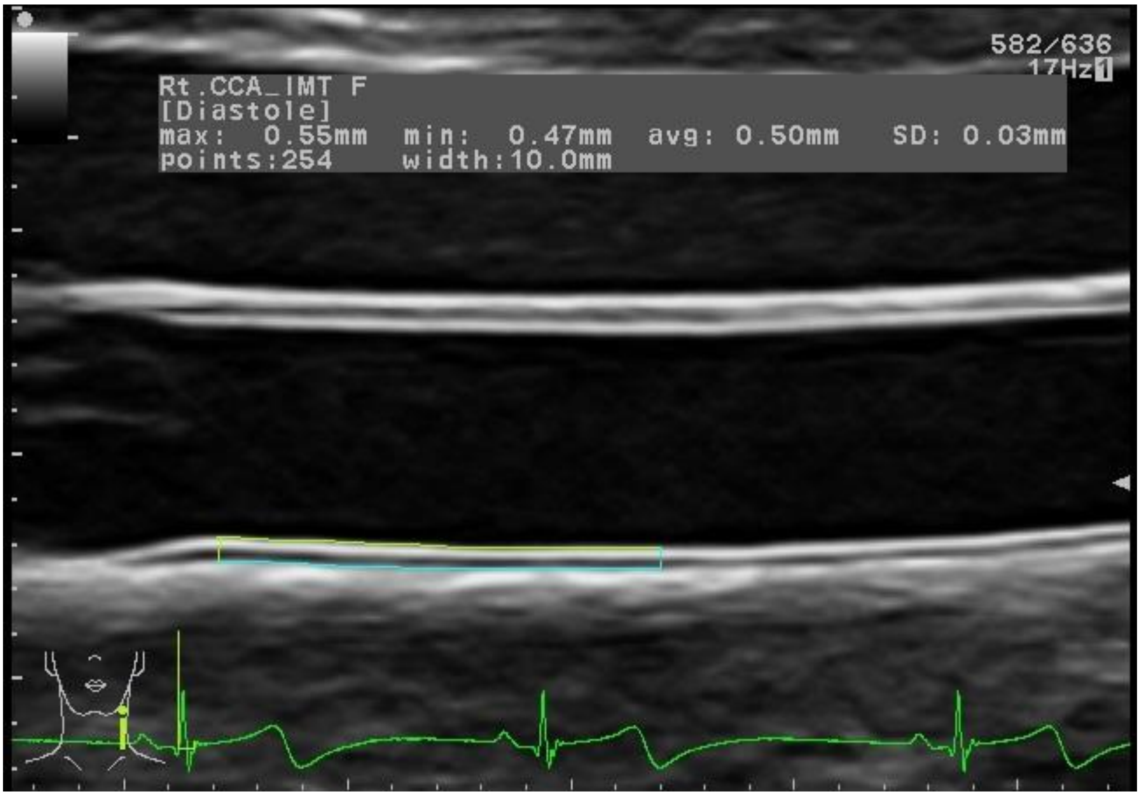

Figure 5. Ultrasound image of the cIMT measurement at the far wall of the CCA

Carotid diameter, cIDR, and parameters of arterial elasticity and stiffness were assessed in M-Mode using the eTracking method of the ProSound Alpha 7. A total of four measurements were performed, two on the right side at an angle of 150° and two on the left at an angle of 210°. The Meijer's Carotid Arc® was used for the exact positioning of the transducer for a standardized measurement at the two angles (137). As in the cIMT measurement, the subjects were in a supine position, and the head was slightly stretched in the opposite direction to the examined side. The measurement location was also directly before the bifurcation of the CCA into the internal and external carotid artery. The cardiac cycle was also recorded with a three-lead ECG. After identifying the bifurcation via the transversal scan, the CCA was observed in the longitudinal scan to make the near and far walls visible. Then the tracking gates were placed at the adventitia-media boundary on the near wall and the media-adventitia boundary on the far wall. With the tracking gates, the vessel motion and, thus, the change in vessel diameter between systole and diastole was recorded over several cardiac cycles (see Figure 6).

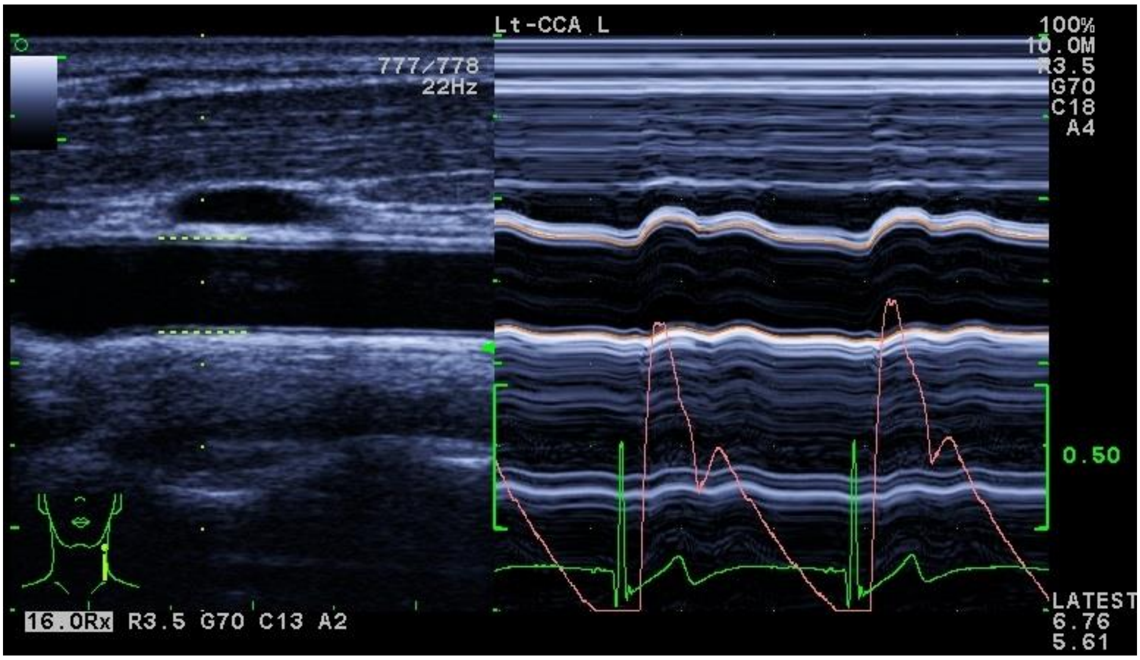

Figure 6. eTracking method for measuring the distension of the CCA

After the loops were saved, the view switched to the measurement view, where five consistent cardiac cycles were selected to calculate the maximum (systolic) and minimum (diastolic) diameter (see Figure 7).

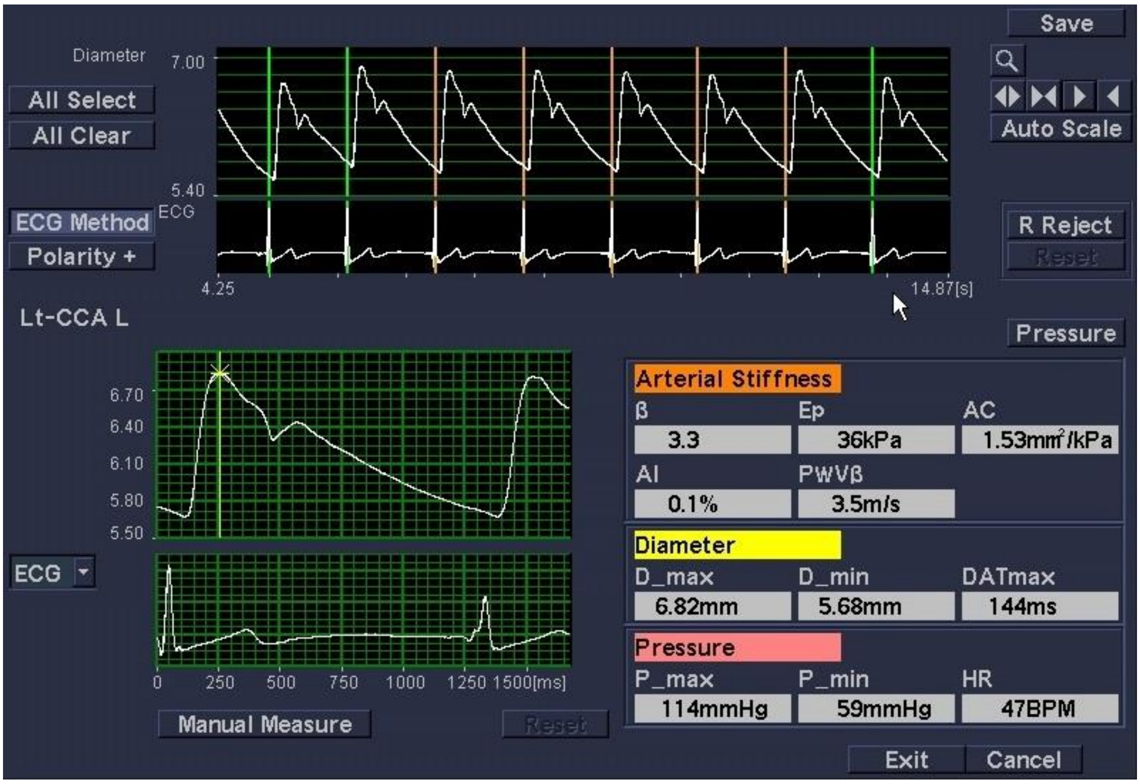

Figure 7. Selection of loops and automatic calculation of stiffness parameters

By calculating the diameter and using the previously measured systolic and diastolic blood pressure, the parameters of carotid elasticity and carotid stiffness were calculated using the following formulas:

$$AC\ (mm^2/kPa) = \pi \frac{(D_{max^2} - D_{min^2})}{4\ (BP_{max} - BP_{min})}$$

$$Ep\ (kPa) = \frac{BP_{max} - BP_{min}}{\frac{D_{max} - D_{min}}{D_{min}}}$$

$$\beta = \frac{\ln \frac{BP_{max}}{BP_{min}}}{\frac{D_{max} - D_{min}}{D_{min}}}$$

$$PWV\beta\ (m/s) = \sqrt{\frac{\beta * BP_{min}}{2\rho}}$$

The parameters of cIMT, carotid elasticity, and carotid stiffness were calculated as an average mean value out of the four measurements. The cIDR was then calculated as the ratio of cIMT and carotid diameter. The parameters were transformed into standard deviation scores using the reference values of Weberruß et al. (138) and Semmler et al. (139).

2.2.3. Physical activity

The physical activity behavior was assessed using the MoMo Physical Activity Questionnaire (MoMo-AFB) for pupils (140). A questionnaire was chosen because different domains (meeting guidelines, exercise in leisure time) and dimensions (mode, frequency, duration, intensity) were asked, many subjects were included, the subjects were healthy children and adolescents, and the personnel and financial budget were limited. It was a single-point measurement (15). The MoMo-AFB records self-reported physical activity with 28 items. Using the questionnaire, minutes per week, minutes in MVPA per week, MET-minutes per week, and MET-hours index of physical activity at school (physical education, additional sports activities at school), in everyday life (working in the garden, working in the household, playing outdoors, walking, non-motorized transportation), in sports clubs, and in leisure time outside the sports club can be calculated. Sport-specific and intensity-dependent MET values are used to calculate the MET-minutes per week and the MET-hours-index (16, 18, 140). The total physical-sporting activity can be calculated using the data on physical activity in school, sports clubs, and leisure time outside the sports club.

Also, the children and adolescents are asked how many of the last seven days they were physically active for at least 60 minutes a day and how many days of a typical week they were physically active for at least 60 minutes a day (141). The mean value of these variables expresses the overall physical activity (activity days per week). In addition, the questionnaire allows an assessment if the WHO recommendation for physical activity is met. This is fulfilled if at least 60 minutes of moderate to vigorous physical activity were performed on all seven days of the last week.

The children and adolescents are asked if they are currently a member of one or more sports clubs, were formerly a member of a sports club but are no longer, or have never been a member of a sports club. Those who are currently members of one or more sports clubs are categorized as club athletes. Regarding the physical activity in sports clubs, the children and young people are asked for each sport whether they participate in competitions in that sport. Those currently competing in at least one sport are categorized as competitive athletes.

Jekauc et al. (142) estimated the reliability and validity of the MoMo-AFB in 196 children and adolescents aged between 9 and 17 years (109 boys, 87 girls). The test-retest reliability and validity were determined using the MVPA variable for each domain. To record the test-retest reliability, the children and adolescents completed the MoMo-AFB twice within seven days. The MoMo-AFB was validated against the Actigraph GT1M and the movement diary Previous Day Physical Activity Recall (PDPAR). The mean Kappa coefficient was between 0.54 ± 0.08 and 0.81 ± 0.08 for all children, between 0.51 ± 0.09 and 0.71 ± 0.11 for boys, and between 0.56 ± 0.08 and 0.88 ± 0.07 for girls. In comparing age groups, the mean kappa coefficient was higher in 14-17-year-olds than in 9-13-year-olds. The lowest mean Kappa coefficients were observed for variable general physical activity, and the highest mean Kappa coefficients for physical activity in sports clubs. The ICC was between 0.60 (physical activity at school) and 0.74 (in the total population, between 0.49 and 0.72 in boys, and between 0.52 and 0.78 in girls. Again, the intra-class-correlation was higher in the 14-17-year-olds than in the 9-13-year-olds. Regarding the criteria-related validity, the correlation of the items of the MoMo-AFB with the ActiGraph GT1M was lower than the correlation with the PDPAR. Overall, the reliability of the MoMo-AFB seems to depend to a certain extent on the age and sex of the children and adolescents. The highest validity is shown in the recording of physical activity in the sports club. Jekauc et al. (142) assign the MoMo-AFB reliability and validity comparable with other (inter-)national activity questionnaires.

3 Publications

This dissertation consists of four publications:

1) Baumgartner, L., Weberruß, H., Oberhoffer-Fritz, R., and Schulz, T. (2020). Vascular Structure and Function in Children and Adolescents: What Impact Do Physical Activity, Health-Related Physical Fitness, and Exercise Have? Front Ped. 8(103). doi: 10.3389/fped.2020.00103 (143)
2) Baumgartner, L., Schulz, T., Oberhoffer, R., and Weberruß, H. (2019). Influence of Vigorous Physical Activity on Structure and Function of the Cardiovascular System in Young Athletes - The MuCAYA-Study. Front Cardiovasc Med. 6, 148. doi: 10.3389/fcvm.2019.00148 (144)
3) Baumgartner, L., Weberruß, H., Appel, K., Engl, T., Goeder, D., Oberhoffer-Fritz, R., et al. (2021). Improved Carotid Elasticity but Altered Central Hemodynamics and Carotid Structure in Young Athletes. Front Sports Act Living. 3(45). doi: 10.3389/fspor.2021.633873 (145)
4) Baumgartner, L., Weberruß, H., Engl, T., Schulz, T., and Oberhoffer-Fritz, R. (2021). Exercise Training Duration and Intensity Are Associated With Thicker Carotid Intima-Media Thickness but Improved Arterial Elasticity in Active Children and Adolescents. Front Cardiovasc Med. 8, 618294. doi: 10.3389/fcvm.2021.618294 (146)

The following articles were published during the doctoral period but are not part of this dissertation:

1) Baumgartner, L., Postler, T., Graf, C., Ferrari, N., Haller, B., Oberhoffer-Fritz, R., et al. (2020). Can School-Based Physical Activity Projects Such as Skipping Hearts Have a Long-Term Impact on Health and Health Behavior? Front Public Health. 8, 352. doi: 10.3389/fpubh.2020.00352 (147)
2) Semmler, L., Weberruß, H., Baumgartner, L., Pirzer, R., and Oberhoffer-Fritz, R. (2020). Vascular diameter and intima-media thickness to diameter ratio values of the carotid artery in 642 healthy children. Eur J Pediatr. doi: 10.1007/s00431-020-03785-3 (139)
3) Weberruß, H., Engl, T., Baumgartner, L., Mühlbauer, F., Shehu, N., and Oberhoffer-Fritz, R. (2022). Cardiac Structure and Function in Junior Athletes: A

Systematic Review of Echocardiographic Studies. RCM. 23(4). doi: 10.31083/j.rcm2304129 (148)

4) Weberruß, H., Baumgartner, L., Mühlbauer, F., Shehu, N., and Oberhoffer-Fritz, R. (2022). Training intensity influences left ventricular dimensions in young competitive athletes. Front Cardiovasc Med. 9. doi: 10.3389/fcvm.2022.961979 (149)

3.1 Article 1

Authors: Lisa Baumgartner, Heidi Weberruß, Renate Oberhoffer-Fritz, Thorsten Schulz

Title: Vascular Structure and Function in Children and Adolescents: What Impact do Physical Activity, Health-Related Physical Fitness and Exercise have?

Journal: Frontiers in Pediatrics

Doi: 10.3389/fped.2020.00103

Summary:

For this article, a non-systematic search was conducted for studies that examined the relationship between vascular properties and physical activity or health-related physical fitness, as well as the effect of exercise on vascular properties in youth. Three of six studies reported positive associations between physical activity and IMT. However, these three studies used questionnaires to assess physical activity. Studies that recorded physical activity with accelerometers found no association with IMT. The association between physical activity and vascular structure seems to depend on the method used to measure activity. Eight studies investigated the relationship between physical activity and vascular stiffness. Again, the results relied on the methods used to assess vascular stiffness and physical activity. Associations of lower vascular stiffness with higher physical activity were found in the combinations of accelerometry and photoplethysmography, accelerometry and applanation tonometry, accelerometry and ultrasound, questionnaire and ultrasound, and questionnaire and photoplethysmography. A clear link was found between health-related physical fitness and vascular structure. Higher health-related physical fitness correlated with lower IMT. The association between health-related physical fitness and vascular stiffness was also significant in most analyzed studies; higher health-related physical fitness was associated with lower vascular stiffness.

Studies using exercise as an intervention observed a reduction in the vascular wall thickness, particularly in study populations with underlying risk factors. However, the effect of the intervention depended on duration and intensity. In four studies, vascular stiffness decreased in pediatric populations with underlying risk factors. The impact could already be observed at moderate intensities. Since exercise includes interventions and targeted exercise to improve physical fitness in sports clubs, this population was also

considered in detail. However, only one study was found that explicitly examined this population. As young athletes are of particular interest concerning cardiovascular adaptation to exercise, this target group should be considered more closely in future studies.

The manuscript was submitted in September 2019, accepted in February 2020, and published in March 2020 in the section *Pediatric Cardiology* of the Journal *Frontiers in Pediatrics.*

Individual Contribution:

Lisa Baumgartner was the principal investigator of this article. Lisa Baumgartner, Heidi Weberruß, and Thorsten Schulz designed the study. Lisa Baumgartner performed the literature search, analyzed the literature, and wrote the manuscript. All authors revised the manuscript and approved the final version.

frontiers in Pediatrics

REVIEW
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Vascular Structure and Function in Children and Adolescents: What Impact Do Physical Activity, Health-Related Physical Fitness, and Exercise Have?

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A physically active lifestyle can prevent cardiovascular disease. Exercise intervention studies in children and adolescents that aim to increase physical activity have resulted in reduced vascular wall thickening and improve cardiovascular function. Here we review the literature that explores the correlations between physical activity, health-related physical fitness, and exercise interventions with various measures of vascular structure and function in children and adolescents. While several of these studies identified improvements in vascular structure in response to physical activity, these associations were limited to studies that relied on questionnaires. Of concern, these findings were not replicated in studies featuring quantitative assessment of physical activity with accelerometers. Half of the studies reviewed reported improved vascular function with increased physical activity, with the type of vascular measurement and the way physical activity was assessed having an influence on the reported relationships. Similary, most of the studies identified in the literature report a beneficial association of health-related physical fitness with vascular structure and function. Overall, it was difficult to compare the results of these studies to one another as different methodologies were used to measure both, health-related physical fitness and vascular function. Likewise, exercise interventions may reduce both arterial wall thickness and increased vascular stiffness in pediatric populations at risk, but the impact clearly depends on the duration of the intervention and varies depending on the target groups. We identified only one study that examined vascular structure and function in young athletes, a group of particular interest with respect to understanding of cardiovascular adaptation to exercise. In conclusion, future studies will be needed that address the use of wall:diameter or wall:lumen-ratio as part of the evaluation of arterial wall thickness. Furthermore, it will be critical to introduce specific and quantitative measurements of physical activity, as intensity and duration of participation likely influence the effectiveness of exercise interventions.

Keywords: vascular structure, vascular function and stiffness, health-related physical fitness, physical activity, exercise, children, adolescents

INTRODUCTION

Cardiovascular disease (CVD) is currently the leading cause of death worldwide; in 2030, CVD may be the major underlying factor in 22.2 million deaths per year (1). To prevent CVD, the American Heart Association recommends adopting a physically active lifestyle, healthy diet and the avoidance of tobacco use (2). Cardiovascular (CV) parameters, including intima-media thickness (IMT) and pulse-wave-velocity (PWV) as subclinical risk maker for CVD, should be monitored at an early age to identify and follow children and adolecents who are at higher risk for CV events (3).

Carotid IMT (cIMT) is an important surrogate marker of subclinical atherosclerosis. It can be assessed using ultrasound at a young age and long before atherosclerotic symptoms occur. Although the incidence of carotid plaques is low in this age group, cIMT may be elevated in children and adolescents with obesity (4, 5), hypertension (6), diabetes (7), cancer (8), or some types of congenital heart disease (9).

The Association for European Paediatric Cardiology Working Group on Cardiovascular Prevention recommends measuring cIMT in pediatric populations using high-resolution ultrasound in two different angels after the carotid bulb of the left and right common carotid artery with a slightly stretched neck and head turned 45° to the opposite side (10). IMT can also be measured at the abdominal aorta as well as at the femoral artery. Of note, arterial diameters can also be measured; these values will permit one to calculate IMT:diameter-ratio (alternatively wall:lumen-ratio) which expresses the relation of wall thickness (IMT) to vascular diameter or lumen, respectively. These ratios are helpful for determining the full impact of physical activity (PA) and other interventions on vascular structure and function.

Vascular compliance is a measure of arterial function that describes the physical adaptation to the blood volume ejected by the left ventricle (LV) and reflects the ability to maintain constant blood flow (11). Vascular stiffness is the reciprocal of vascular compliance and is defined by different parameters such as elastic modulus or pulse wave velocity (PWV). Vascular stiffness can be measured with ultrasound, oscillometric devices, photoplethysmography, and/or applanation tonometry applied to the aorta, femoral, brachial or carotid arteries. Parameters measured with this devices include compliance, distensibility, stiffness index, reflection index, elastic modulus, augmentation index (AI), and PWV. Pediatric populations with elevated cardiovascular risk can present reduced compliance or increased stiffness, for example children with hypertension (12), obesity (12, 13), hypercholesterolemia (14), metabolic syndrome (15), diabetes (16), and congenital heart disease (17).

Abbreviations: AI, augmentation index; AI@75, augmentation index at heart rate 75/min; aIMT, aortic intima-media thickness; cIMT, carotid intima-media thickness; CRF, cardiorespiratory fitness; CVD, cardiovascular disease; HIIT, high-intensity intermittent training; HRPF, health-related physical fitness; IMT, intima-media thickness; LPA, light physical activity; LTPA, leisure-time physical activity; LV, left ventricle; MET, metabolic equivalent; MPA, moderate physical activity; MVPA, moderate-to-vigorous physical activity; PA, physical activity; PWV, pulse wave velocity; SED, sedentary behavior; VPA, vigorous physical activity.

TABLE 1 | Description of MET and activity intensity levels.

MET	1 MET = consumption of 3.5 ml O_2 per kilogram body mass per minute at rest (25)
SED	≤1.5 METs during sitting, reclining or lying position (26)
LPA	<3.0 METs, e.g., walking slowly, washing dishes or playing darts (27)
MPA	3.0–6.0 METs, e.g., washing windows, golf, recreational badminton (27)
VPA	>6.0 METs, e.g., jogging, cross-country skiing, soccer (27)
MVPA	≥3 METs

MET, metabolic equivalent; SED, sedentary behavior; LPA, light physical activity; MPA, moderate physical activity; VPA, vigorous physical activity; MVPA, moderate-to-vigorous physical activity.

PA and health-related physical fitness (HRPF) are both associated with a lower risk of CVD in adulthood (18, 19). The results of several recent studies suggest a critical role for PA and HRPF in promoting healthy vascular structure and function in children and adolescents (20, 21). Interventions that include endurance or resistance exercises have also been introduced in an attempt to improve impaired vascular structure and function in pediatric populations at risk (22, 23).

This review provides an overview of the relationship between PA and HRPF with vascular structure and function in children and adolescents. Exercise is a planned and structured PA to improve activity level and HRPF. Therefore, this review further discusses the effect of exercise on vascular structure and function in intervention studies and young athletes. We searched in several databases for articles published between 2005 and June 2019 using the keywords "intima-media thickness," "arterial structure," "arterial diameter," "vascular function," "arterial stiffness," "exercise," "physical activity," "physical fitness," "cardiorespiratory fitness," "athlete," "child*," or "adolesc*." We did not include a discussion of biochemical parameters of endothelial function in the review.

PHYSICAL ACTIVITY

PA is any movement of the body that is produced by skeletal muscles and that requires energy expenditure (24). Regular PA has a cardioprotective effect on health not only in youth but also later in life. Therefore, children should adopt a physically active lifestyle at an early age and maintain it throughout life. The World Health Organization recommends that children and adolescents undertake moderate-to-vigorous physical activity (MVPA) for at least 60 min per day (**Table 1**) (24). MVPA is commonly assessed as self-reporting using specific questionnaires. While this method is simple, the data that result may be inaccurate due to recall bias (28). Accelerometer and related wearable instruments permit collection of more objective data, as these devices do not depent on self-assessment. PA measurements vary by design and as per the individual goal for the research program (29).

Vascular Structure

We identified six published studies that explored correlations between PA and vascular structure (**Table 2**); four of these reports are included in the literature review published in 2016 by Cayres et al. (41). Three of the six studies used accelerometers to measure PA (20, 33, 37) and three relied on questionnaires (31, 35, 36).

Among the results of the questionnaire-based studies, Idris et al. (31) found no relationship between time-weighted metabolic equivalents (MET, **Table 1**) and cIMT but identified lower cIMT in association with higher values of time-weighted sports-related MET among the 5-year old participants. Likewise, Pahkala et al. (35) found that leisure-time physical activity (LTPA) had a beneficial impact on aortic IMT (aIMT); specifically, a moderate increase in LTPA among sedentary 13 and 15 year olds was associated with a significant decreased progression of aIMT. In a similar study, Pahkala et al. (36) reported no direct association between LTPA and cIMT or aIMT, although 17-year olds with high levels of LTPA overall experienced lower levels of aIMT compared to those with low LPTA in relation to their fitness level.

By contrast, among the studies that made use of accelerometers, Ried-Larsen et al. (20, 37) reported no correlation between MVPA or vigorous PA (VPA) and cIMT in a study of 8-to-10-year old Danish children; analogous results were obtained from adolescents with a mean age of 15.6 ± 0.4 years. Similary, Melo et al. (33) found that sedentary behavior (SED) and MVPA were not definitively related to cIMT in 11- to-13-year-old Portuguese children and adolescents.

In summary, we conclude that studies that used questionnaires identified correlations between PA and healthy vascular structure, but no such relationship emerged from studies that employed accelerometers. As such, it is clear that associations between PA and vascular structure may depend all or in part on the method used to assess activity. Nonetheless, three out of six studies reported beneficial associations between PA and cIMT or aIMT.

Vascular Function

We identified eight studies that examined the relationships between PA and vascular function; five of these studies used questionnaires (31, 32, 38–40) and three (20, 30, 34) used accelerometers to assess PA in children and adolescents.

Moderate PA (MPA), VPA and cumulative time spent in PA, specifically data documenting individuals achieving above 3–7 METs, were inversely associated with stiffness index, measured at the finger tip by pulse contour analysis. Of note, children participating in PA who achieved 3 METs/day presented with lower stiffness index values (30). Nettlefold et al. (34) found no association between PA and compliance of the large arteries, but did report higher compliance of small arteries with increased time spent in light PA (LPA), MPA, or MVPA per day. Likewise, Ried-Larsen et al. (38) found that boys who ride bicycles every day have lower young's elastic modulus, higher distensibility, and higher arterial compliance compared to boys who ride fewer than three times per week. Likewise, boys who traveled to school by bicycle had higher compliance and lower young's elastic modulus compared to those who use passive transportation (38).

In other studies, more time spent in unstructured PA was related to lower stiffness index in children between 6 and 8 years of age (39). However, Ried-Larsen et al. (37) did not identify a direct association between time spent in MVPA and carotid compliance, distensibility, young's elastic modulus, and stiffness index; there was also no statistical relationship between VPA and compliance, distensibility, young's elastic modulus, and stiffness index. However, boys classified in the highest quartile of MVPA had significantly lower young's elastic modulus and stiffness index compared to boys in the lowest quartile.

By contrast, carotid distensibility and carotid elastic modulus were associated with neither total time-weighted MET, sports time-weighted MET nor organized sport time-weighted MET in children (31). Furthermore, parameters relating to vascular stiffness were not associated with time spent in MVPA in a daily basis and VPA in children and adolescents (20). VPA (categorized in tertiles) had no impact on carotid-femoral PWV nor on aortic AI (40). Kochli et al. (32) also found no association between aortic PWV and VPA, indoor or outdoor activity.

In conclusion, of the eight studies that explored the association between PA and vascular stiffness, four reported improved vascular function with increased PA; two of these studies reported accelerometer findings and two used questionnaires. Of importance, none of the studies identified any unfavorable associations between PA and vascular stiffness. The two studies which used photoplethysmography reported significant lower stiffness indices in association with higher levels of PA (30, 39). The four studies reported ultrasound measurements of vascular parameters and the study which used PA questionnaires all report an inverse correlation between PA and vascular stiffness (38); this result was not reported in the two studies which used accelerometers for measuring PA (20, 37). Of the studies which used applanation tonometry to measure vascular stiffness, only Nettlefold et al. (34) reported better vascular elasticity with increasing PA; of note, this study featured accelerometer findings to report PA in contrast to the report from Walker et al. (40) which used a questionnaire. Hence, the type of vascular measurement employed and the means by which PA was assessed may have an influence on the relationships reported. Of note, the number of study participants in each study may also have an influence on the results obtained.

HEALTH-RELATED PHYSICAL FITNESS

HRPF includes cardiorespiratory fitness (CRF), muscular endurance, muscular strength, flexibility, and body composition and is an important indicator of health and well-being (42). The following studies focus on CRF or strength and include healthy children and adolescents only and exclude those with chronic conditions including overweight, obesity or diabetes.

Vascular Structure

The majority of the studies included in this review used ergometers to measure HRPF (**Table 3**) and include results from single trails that include a 20 m shuttle run, handgrip strength test, curl-ups, and push-ups.

Among Portuguese children between the ages of 11 and 13 years, cIMT was inversely associated with CRF independent of

TABLE 2 | Overview of studies that evaluated associations of physical activity and vascular structure and function.

References	*N*	Age	Measurement of PA	Vascular measurement	Parameter of vascular structure	Parameter of vascular function	Results	Statistics
Haapala et al. (30)	136	6–8	Combined heart rate and accelerometer	Photoplethysmography		Stiffness index	↓stiffness index with ↑MPA	$\beta = -0.273$, 95% CI–0.448 to–0.097, $p = 0.003$
							↓stiffness index with ↑VPA	$\beta = -0.254$, 95% CI–428 to–0.080, $p = 0.005$
							↓stiffness index with cumulative time spent in PA > 3 METs	$\beta = -0.279$, 95% CI–0.453 to–0.106, $p = 0.002$
							↓stiffness index with cumulative time spent in PA > 4 METs	$\beta = -0.341$, 95% CI–0.515 to–0.167, $p < 0.001$
							↓stiffness index with cumulative time spent in PA > 5 METs	$\beta = -0.349$, 95% CI–0.524 to–0.174, $p < 0.001$
							↓stiffness index with cumulative time spent in PA > 6 METs	$\beta = -0.312$, 95% CI–0.220 to–0.064, $p < 0.001$
							↓stiffness index with cumulative time spent in PA > 7 METs	$\beta = -0.254$, 95% CI–0.428 to–0.080, $p = 0.005$
Idris et al. (31)	595 237	5 8	Questionnaire	Ultrasound	cIMT	Carotid distensibility Carotid elastic modulus	No association of total MET and vascular parameters	-
							↓cIMT with ↑sport time-weighted MET at 5yrs	−3.20 mm/SD, 95% CI–6.34 to–0.22, $p = 0.04$
							No association of organized sport time-weightes MET at 5yrs	-
							No association of total, sport and organized sport time-weights MET at 8yrs	-
Kochli et al. (32)	1171	6–8	Questionnaire	Oscillometric device		Aortic PWV	No association of VPA, indoort and outdoor activity and aortic PWV	-
Melo et al. (33)	265	11–13	Accelerometer	Ultrasound	cIMT		No association of SED and MVPA with cIMT	-
Nettlefold et al. (34)	102	8–11	Accelerometer	Applanation tonometry		Compliance of small and large arteries	No association of PA, MPVA, SED, LPA, MPA and VPA and compliance of large arteries	-
							↑compliance of small arteries with ↑LPA	$p = 0.003$
							↑compliance of small arteries with ↑MPA	$p = 0.036$
							↑compliance of small arteries with ↑MVPA	$p = 0.043$
Pahkala et al. (35)	553 531 494	13 15 17	Questionnaire	Ultrasound	aIMT		↓aIMT with ↑LTPA	$\beta \pm SD = -0.00034 \pm 0.00014$, $p = 0.011$

(Continued)

TABLE 2 | Continued

References	*N*	Age	Measurement of PA	Vascular measurement	Parameter of vascular structure	Parameter of vascular function	Results	Statistics
Pahkala et al. (36)	449-467	17	Questionnaire	Ultrasound	aIMT, cIMT		↓progression of aIMT with a moderate increase in LTPA between 13 and 17	$p = 0.047$
							No association between aIMT and LTPA	-
							No association between cIMT and LTPA	-
							↓aIMT in high LTPA compared to low LTPA concerning fitness level	$p = 0.019$
Ried-Larsen et al. (37)	397	15.6±0.4	Accelerometer	Ultrasound	cIMT	Carotid compliance Carotid distensibility Carotid YEM Stiffness index	No association between MVPA, VPA and vascular parameters	-
							Lower carotid YEM in the highest quartile of MVPA in boys	$p < 0.05$
							Lower stiffness index in the highest quartile of MVPA in boys	$p < 0.05$
Ried-Larsen et al. (20)	254	8–10	Accelerometer	Ultrasound	cIMT	Carotid compliance Carotid distensibility Carotid YEM Stiffness index	No association between MVPA or VPA and vascular parameters	-
Ried-Larsen et al. (38)	375	15.7±0.4	Questionnaire	Ultrasound		Carotid compliance Carotid distensibility Carotid YEM	↑carotid compliance in boys who practice bicycling every day	$\beta = 0.44$, 95% CI 0.08 to 0.81, $p = 0.02$
							↑carotid distensibility in boys who practice bicycling every day	$\beta = 0.40$, 95% CI 0.02 to 0.77, $p = 0.04$
							↓carotid YEM in boys who practice bicycling every day	$\beta = -0.50$, 95% CI−0.86 to−0.13, $p = 0.01$
							↑carotid compliance in boys who use bike for traveling to school	$\beta = 0.59$, 95% CI 0.08 to 1.01, $p = 0.02$
							↓carotid YEM in boys who use bike for traveling to school	$\beta = -0.54$, 05% CI−1.07 to−0.02, $p = 0.045$
							No associations in girls	-
Veijalainen et al. (39)	160	6–8	Questionnaire	Photoplethysmography		Stiffness index reflection index	↓stiffness index with ↑unstructured PA	$\beta = -0.162$, $p = 0.042$
							No association of stiffness index and total PA and recess PA	-
							No association between reflection index and unstructured, total and recess PA	-
Walker et al. (40)	485	12–14	Questionnaire	Applanation tonometry		Carotid-femoral PWV Aortic AI	No association of carotid-femoral PWV and aortic AI with PA	-

PA, physical activity; Cimt, carotid intima-media thickness; aIMT, aortic intima-media thickness; PWV, pulse wave velocity; YEM, young's elastic modulus; AI, augmentation index; MPA, moderate physical activity; VPA, vigorous physical activity; MVPA, moderate to vigorous physical activity; MET, metabolic equivalent; SED, sedentary behavior; LPA, light physical activity; LTPA, leisure time physical activity.

TABLE 3 | Overview of studies that evaluated associations of health-related physical fitness and vascular structure and function.

References	*N*	Age	Measurement of HRPF	Vascular measurement	Parameter of vascular structure	Parameter of vascular function	Results	Statistics
Agbaje et al. (43)	329	8–11	Ergometer test	Photoplethysmography		Stiffness index	↑reflection index with ↑CRF in boys	$\beta = 0.377$, $p = 0.001$
							↑reflection index with ↑CRF in girls	$\beta = 0.337$, $p = 0.02$
							no association between stiffness index and CRF	
Farr et al. (44)	96	9–10	Ergometer test	Applanation tonometry		peripheral non-transformed index carotid-ankle PWV carotid-radial PWV	no linear association between vascular parameters and CRF	-
							↑carotid-ankle PWV in higher CRF group compared to lower CRF group	$p < 0.05$
							no differences in periperhal non-transformed index and carotid-radial PWV betweeh higher and lower CRF group	-
Kochli et al. (32)	1171	6–8	20 m shuttle run	Oscillometric device		Aortic PWV	↓aortic PWV with ↑CRF	$\beta = -0.024$, 95% CI–0.035 to–0.012, $p < 0.001$
Melo et al. (33)	265	11–13	Ergometer test	Ultrasound	cIMT		↓cIMT with ↑CRF	$\beta = -0.13$, $p = 0.04$
Melo et al. (45)	336	11–12	Hand grip	Ultrasound	cIMT carotid artery diameter		↓cIMT in middle and high strength group compared to low strength group	$p < 0.05$
							no differences in carotid artery diameter between strength groups	
Melo et al. (46)	413	11–12	Ergometer test	Ultrasound	cIMT		OR of 2.8 for unfit children having increased cIMT	95% CI 1.40 - 5.53
Meyer et al. (47)	646	13.9±2.1	6 min run	Oscillometric device		Aortic PWV Aortic AI@75	↑aortic PWV with ↑CRF	$\beta = 0.173$, $p < 0.001$
							↓aortic AI@75 with ↑CRF	$\beta = -0.106$, $p = 0.025$
Pahkala et al. (36)	449–467	17	Ergometer test	Ultrasound	aIMT, cIMT	Aortic distensibility Carotid distensibility Aortic young's elastic modulus Carotid young's elastic modulus	↓aIMT with ↑CRF	$\beta = -0.0029 \pm 0.0013$, $p = 0.031$
							no association between cIMT and CRF	
							↓aortic young's elastic modulus with ↑CRF	$\beta = -0.012 \pm 0.0053$, $p = 0.025$
							no association with distensibility and carotid young's elastic modulus	-
Reed et al. (48)	99	9–11	20 m shuttle run	Applanation tonometry		Compliance of large and small arteries	↑compliance of large arteries and CRF	not available
							↑compliance of small arteries and CRF	not available
							↑compliance of large arteries in quartile 4 compared to quartile 1 and 2	$p < 0.05$
							↑compliance of small arteries in quartile 4 compared to quartile 2	$p < 0.05$

(Continued)

TABLE 3 | Continued

References	*N*	Age	Measurement of HRPF	Vascular measurement	Parameter of vascular structure	Parameter of vascular function	Results	Statistics
Ried-Larsen et al. (37)	397	15.6±0.4	Ergometer test	Ultrasound	cIMT	Carotid compliance Carotid distensibility Carotid young's elastic modulus Stiffness index	no association between cIMT and carotid compliance and CRF	-
							↓carotid young's elastic modulus with ↑CRF	$\beta = -16.38$, 95% CI−27.16 to−5.60, $p = 0.003$
							↑carotid distensibility with ↑CRF	$\beta = 0.24$, 95% CI 0.01 to 0.47, $p = 0.037$
							↓stiffness index with ↑CRF in boys	$\beta = -0.28$, 95% CI−0.55 to−0.01, $p = 0.049$
							↓carotid young's elastic modulus in quartiles 2, 3 and 4 compared to quartile 1	$p < 0.05$
							↓stiffness index in quartiles 3 and 4 compared to quartile 1	$p < 0.05$
							higher carotid distensibility in quartiles 3 and 4 compared to quartile 1	$p < 0.05$
Sakuragi et al. (49)	573	10.1±0.3	20 m shuttle run	Applanation tonometry		Carotid-femoral PWV	↓carotid-femoral PWV with ↑CRF	$\beta = -0.047$, 95% CI−0.07 to−0.024, $p < 0.001$
Veijalainen et al. (39)	160	6–8	Ergometer test	Photoplethysmography		Stiffness index Reflection index	↓stiffness index with ↑CRF	$\beta = -0.246$, $p = 0.006$
							no association between reflection and CRF	-
Weberruss et al. (21)	697	7–17	20 m shuttle run Curl-ups Push-ups	Ultrasound	cIMT	Carotid elastic modulus Carotid compliance Stiffness index β PWV β	↑cIMT with ↑CRF	$\beta = <0.001 \pm 0$, $p < 0.001$
							↑carotid compliance with ↑CRF	$\beta = 0.004 \pm 0.001$, $p < 0.001$
							↓stiffness index β with ↑CRF	$\beta = -0.01 \pm 0$, $p < 0.001$
							↓PWV β with ↑CRF	$\beta = -0.01 \pm 0$, $p < 0.001$
							↓carotid elastic modulus with ↑CRF	$\beta = -0.12 \pm 0.03$, $p < 0.001$
							↑carotid elastic modulus in low fit group	$p = 0.009$
							↑stiffness index β in low fit group	$p = 0.03$
							↑ PWV β in low fit group	$p = 0.005$
							no associations with curl-ups and push-ups	-

cIMT, carotid intima-media thickness; aIMT, aortic intima-media thickness; PWV, pulse wave velocity; CRF, cardiorespiratory fitness; AI, augmentation index.

age, sex, maturity, SED, and MVPA (33) and values of maximum oxygen uptake revealed an inverse correlation with aIMT (36). Furthermore, participants identified as "low-fit" at the age of 11 experienced accelerated progression of aIMT between ages of 11 and 17 years (36).

By contrast, in a study involving 697 children and adolescents between 7 and 17 years, Weberruss et al. (21) found a significant positive correlation between cIMT and CRF. CRF was measured with a 20m shuttle run, which means that the participant runs between two lines (20m distance) with a given speed. The speed is stepwise increased and the time will be stopped if the participant does not touch the line in the given speed. In contrast, Pahkala et al. (36) observed no associations between these parameters; diminished CRF was not associated with increased risk of having cIMT. No association of a maximal load test on a cycle ergometer and cIMT was reported in Danish adolescents (37) but Melo et al. (46) reported an OR of 2.8 in unfit children for having a cIMT ≥ 75th percentile.

Muscular strength has also been evaluated as a parameter contributing to HRPF. Among 11- to 12-year old Portuguese children, carotid artery diameter did not differ between children with low, middle or high muscle strength index; but children with middle to high muscle strength index as measured using a handgrip test showed lower values of cIMT compared to those measured in children with low muscular strength (45). By contrast, muscular strength determined in a series of German children and adolescents (push-ups and curl-ups) was not associated with CRF (21).

Taken together, the literature reveals a significant relationship between HRPF and vascular structure in population-based studies that include children and adolescents; in general, higher performance in HRPF tasks corresponds to lower levels of IMT. One study did reveal an inverse correlation between CRF and aIMT but not with cIMT. The authors hypothesize that structural alterations such as IMT may begin in the aorta and progress in the carotid artery later in life (36, 50).

Interestingly, the association between HRPF and vascular structure has occurred primarily in children and adolescents with increased cardiovascular risk; by contrast, the participants in most published studies are their healthy peers. For example, Ried-Larsen et al. (37) enrolled only healthy participants and excluded those who were chronically ill; this may explain the absence of associations observed between cIMT and CRF in this study. Arteries of fit children and adolescents may undergo adaptation to exercise, a process which may have an impact on smooth muscle cells in the vascular media; this adaptation may explain the positive relationship of cIMT to CRF observed by Weberruss et al. (21). Nevertheless, at this time there is no clear association between HRPF (evaluated as muscular strength) and vascular structure; further investigation is warranted.

Vascular Function

We identified ten studies which explored the association between HRPF and arterial function in children and adolescents; five studies featured a (maximal) ergometer test, one included a 6-min run, three studies included the 20 m shuttle run, and one study explored responses to a combination of the 20 m shuttle run, curl-ups and push-ups. The studies applied numerous methods to measure vascular stiffness (ultrasound, oscillometric device, photoplethysmography, applanation tonometry) and included a wide range of stiffness parameters.

In the first group of studies, CRF was inversely and therefore beneficially associated with aortic PWV but the association became non-significant when the model was further adjusted for blood pressure (32). Carotid PWV (21) and carotid-femoral PWV (49) were both inversely related to CRF adjusted for blood pressure. Farr et al. (44) reported no direct correlation between CRF and carotid-ankle PWV, carotid-radial PWV or peripheral non-transformed index but when devided into a higher and lower group of CRF, subjects in the higher group of CRF had higher carotid-ankle-PWV compared to the lower group. By contrast, another study reported increased aortic PWV in association with higher CRF in children and adolescents between the ages of 11 and 17 years (47). Three of four studies observed a significant favorable association between CRF and stiffness index (21, 37, 39, 43).

Two studies used non-invasive photoplethysmography and assessed reflection index as parameter of vascular function; one identified no correlations between the reflection index and CRF (39), one reported a positive association between reflection index and CRF in boys and girls (43). Pahkala et al. (36) reported an inverse correlation between CRF and young's elastic modulus for the aorta but not for the carotid artery among a group of 17-years olds. Furthermore, Weberruss et al. (21) documented a favorable association between CRF and carotid elastic modulus while Ried-Larsen et al. (37) reported a significant inverse correlation between CRF and carotid elastic modulus.

By contrast, aortic distensibility was not associated with CRF (36). Two studies investigated the associations between carotid distensibility and CRF; only Ried-Larsen et al. (37) reported a positive relationship (36, 37). Two of the three studies documented a positive association between carotid arterial compliance and CRF (21, 37, 48), while aortic AI@75 (the AI at a standardized heart rate of 75 beats per minute) was inversely associated with CRF (47).

Only one study investigated the relationship between muscle strength (push-up and curl-ups) and CRF; no associations with vascular function were identified when evaluating these parameters (21).

Several studies compared levels of CRF to specific stiffness parameters. Reed et al. (48) evaluated this relationship and found significantly lower compliance in large arteries in the first (up to 10 laps) and second quartile (21 to 32 laps) compared to the highest quartile (more than 43 laps) of CRF, recorded with a 20 m shuttle run; compliance of small arteries was lower in the second quartile of CRF compared to the fourth quartile.

Ried-Larsen et al. (37) divided CRF in four quartiles and observed significant lower carotid young's elastic modulus in the second to fourth quartiles compared to the first quartile; these results indicate stiffer arteries at lower fitness levels. Likewise, stiffness index was higher in the first quartile compared to the third and fourth quartile, and adolescents in CRF quartiles three and four showed significantly higher carotid compliance compared to adolescents within the first quartile. In a related study, very fit children and adolescents (>80th percentile) had lower elastic modulus, stiffness index and carotid PWV than low fit (<20th percentile) children and adolescents (21).

To summarize, most of the studies reported a beneficial association between vascular stiffness and CRF among children and adolescents; these findings are consistent with those reported in studies of, young, middle-aged and older adults (51–53). Nevertheless, it was difficult to compare studies to one another because of different methods used to measure both HRPF and vascular stiffness. Of interest, all studies, in which the 20 m shuttle run was used to assess HRPF, revealed a favorable association between stiffness parameters and HRPF.

EXERCISE

Children and adolescents with obesity or hypertension typically have impaired arterial structure and function. Several groups have introduced intervention methods in an attempt to alter the vascular architecture among subjects in these groups. Besides, exercise also refers to children and adolescents who perform at a sustained level in organized sports club activities.

Vascular Structure

Garcia-Hermoso et al. (54) published a comprehensive meta-analysis that included six studies that focused on the impact of aerobic, resistance or both aerobic and resistance exercises on vascular structure in obese populations aged between 6 and 18 years. Four of these studies (three aerobic, one aerobic, and resistance exercises) resulted in reductions in cIMT. Overall, the results indicate the changes in cIMT that result from exercise interventions were small to moderate ($g = -0.306$; 95% CI :−0.540 to −0.072, $p = 0.011$) with higher impact achieved in response to the longer interventions. Cayres et al. (41) also conclude that there are beneficial effects of exercise interventions on cIMT, but note that there are very few studies that examine interventions in healthy, non-obese populations.

In addition to these observations, there are several more recent interventional studies investigated that explore the impact of exercise on vascular structure (**Table 4**). For example, obese boys were subjected to a 12-week high-intensity intermittent training (HIIT) of 8 × 2 min at 90% peak power output or a supra-HIIT of 2 × 20 s at 170% peak power output; these strategies resulted in significant reductions in cIMT of 0.02 mm in both intervention groups, but had no impact on the diameter of the brachial artery (55).

By contrast, seven children with type 1 diabetes mellitus were enrolled in an 18-week interval running intervention (30 min intervention, 10 min cool-down, two sessions per week); no significant changes in carotid artery diameter, cIMT or wall:lumen-ratio were detected (56).

To the best of our knowledge, there is only one published study that investigated the impact of an exercise intervention (high-intensity interval training) in a school-based population; this study also revealed no significant reduction in cIMT after 10 weeks (60). However, in young adolescent male wrestlers, cIMT measurements were significantly lower when compared to age- and sex-matched controls (61).

Taken together, the published results suggest that exercise interventions in groups of young participants may result in reduced thickening of the arterial walls, but the overall impact depends on duration and intensity of the intervention and the nature of the target groups. Given the current prevalence of overweight and obesity among children and adolescents, future population-based studies are needed to determine definitively whether exercise leads to an improved vascular health in these populations.

Vascular Function

Exercise interventions on obese and/or prehypertensive children and adolescents have shown promising results toward the goal of reducing arterial stiffness. The study noted earlier in which 48 obese boys were challenged with a 12-week HIIT or supra-HIIT resulted in significant reductions in brachial PWV in both intervention groups (55). In another study, a combined resistance and aerobic exercise intervention (50 min, three times per week) in prehypertensive adolescent girls resulted in significant reductions in brachial-ankle PWV after 12 weeks (57). Similarly, a rope-jumping intervention (50 min, five times per week) resulted in reduced brachial-ankle PWVs in a study with obese prehypertensive girls (23). Likewise, Wong et al. (58) found that combined resistance and aerobic exercise (60 min, 3 times per week) in obese girls led to a significant reduction of brachial PWV compared to a control group after three months.

By contrast, Horner et al. (22) found no change in aortic PWV in obese adolescents who participated in aerobic (treadmill training, 60–75% of VO_{2peak}) or resistance (whole-body exercises) interventions for a period of three months. Moreover, Hacke et al. (59) implemented preschool exercise lessons (45 min, two times per week for six months) but was unable to detect any improvement in aortic PWV in the intervention group compared to controls.

We identified only one study that evaluated vascular function in young athletes; this study reported no significant differences in arterial compliance, distensibility and elastic modulus among young adolescent male wrestlers vs. age- and sex-matched controls (61).

In summary, four out of five studies that we evaluated were conducted in children and adolescents with increased cardiovascular risk (obesity, hypertension), reported reductions in vascular stiffness after an exercise intervention. As such, we can conclude that exercise interventions with at least moderate levels of intensity can reduce vascular stiffness among pediatric populations at risk. Horner et al. (22) and Hacke et al. (59) reported no reductions in body mass index in response to these interventions; improvement in vascular function might be linked to a change in anthropometric parameters. It is also possible that the intensity of their intervention was too low to promote measurable changes in vascular function. The need to implement exercise programs in order to improve the health of an increasing number of inactive children and adolescents is supported globally. Further studies should take into account the intensity and duration of interventions to improve the design and therefore effectiveness of these programs.

TABLE 4 | Overview of studies investigating the impact of exercise on vascular structure and function.

References	*N*	Age	Intervention	Duration of intervention	Vascular measurement	Parameter of vascular structure	Parameter of vascular function	Results	Statistics
STUDIES IN PEDIATRIC POPULATIONS AT RISK									
Chuensiri et al. (55)	48 obese boys (16 HIIT, 16 supra-HIIT, 16 controls)	8–12	HIIT (8 × 2 min at 90% peak power output)supra-HIIT (2 × 20 s at 170% peak power output)	3 times per week, 12 weeks	Ultrasound, automatic vascular screening device	cIMT brachial artery diameter	brachial PWV	↓brachial PWV in HIIT ↓brachial PWV supra-HIIT mo time*group interaction in brachial PWV ↓cIMT in HIIT ↓cIMT in supra-HIIT mo time*group interaction in cIMT no change in brachial artery diameter	$p < 0.05$ $p < 0.05$ - $p < 0.05$ $p < 0.05$ - -
Horner et al. (22)	81 obese adolescents (30 aerobic exercise, 27 resistance exercise, 24 controls)	12–18	Aerobic exercise: 60 min moderate training on treadmill, elliptical or ergometer resistance exercise: 10 whole-body exercises (8–12 repetitions)	3 times per week, 3 months	Ultrasound, automatic device	cIMT	aortic PWV	no change in cIMT no change aortic PWV	- -
Seeger et al. (56)	7 DMI children	10.9 ± 1.5	30 min interval running and 10 min warm-up and cool-down	2 times per week, 18 weeks	Ultrasound	cIMT carotid artery diameter wall:lumen-ratio		no changes in parameters of arterial structure	-
Son et al. (57)	40 obese prehypertensive girls (20 intervention, 20 controls)	15 ± 1	60 min combined resistance and aerobic exercise	3 times per week, 12 weeks	Applanation tonometry		brachial PWV	↓brachial PWV in intervention group	$p < 0.05$
Sung et al. (23)	40 obese prehypertensive girls (20 intervention, 20 controls)	14–16	5 min warm-up, 40 min rope jumping variations, 5 min cool-down	5 times per week, 12 weeks	Applanation tonometry		brachial PWV	↓brachial PWV in intervention group	$p \leq 0.05$
Wong et al. (58)	30 obese girls (15 intervention, 15 controls)	15.2 ± 1.2 15.3 ± 1.1	60 min combined resistance and aerobic exercise	3 times per week, 12 weeks	Applanation tonometry		brachial PWV	↓brachial PWV in intervention group	$p < 0.05$
POPULATION-BASED STUDIES									
Hacke et al. (59)	135 pre-schoolers (92 intervention group, 43 controls)	4.8 ± 0.8	45 min exercise lessons	2 times per week, 6 months	Oscillometric device		aortic PWV	no change in aortic PWV	-
Weston et al. (60)	101 adolescents (41 intervention, 60 controls)	14.0 ± 0.3	4 to 7 repetitions of 45 s drills (soccer, dance, boxing, basketball) and 90 s recovery	3 times per week, 10 weeks	Ultrasound	cIMT		no change in cIMT	-
STUDIES IN YOUNG ATHLETES									
Demirel et al. (61)	33 elite male wrestlers 35 matches controls	15.9 ± 0.9 16.0 ± 0.8			Ultrasound Applanation tonometry	cIMT	arterial compliance arterial distensibility diastolic wall stress elastic modulus	↓cIMT in athletes ↑diastolic wall stress in athletes no difference in compliance no difference in distensibility no difference in elastic modulus	$p = 0.01$ $p = 0.03$ - - -

HIIT, high-intensity intermittent training; DMI, diabetes mellitus type 1; cIMT, carotid intima-media thickness, PWV, pulse wave velocity; AI, aortic augmentation index.

CONCLUSION

In conclusion, PA and HRPF are directly associated with improved vascular structure and function in children and adolescents as determined in population-based studies. Furthermore, interventions in pediatric populations at risk reveal promising results that suggest a role for moderate exercise in correcting early increases in vascular wall thickness and vascular stiffness.

The results of our study are comparable with the findings of adult studies. Here Thijssen et al. (62) showed in a comprehensive review that both physical activity and HRPF are inversely related to cIMT and that movement interventions lead to a significant reduction in wall thickness of the carotid, femoral and brachial arteries. The identical direction of the results was also observed in the correlation between activity, fitness and exercise and vascular function in adults (63–65).

It was difficult to perform critical comparisons among these studies given the variety of methods and measurements employed, especially in studies that measured vascular function. Elmenhorst et al. (66) compared carotid PWV measured by ultrasound and aortic PWV measured by an oscillometric device and found significant lower values of carotid PWV (4.01 $\pm$ 0.44 m/s) compared aortic PWV (4.67 $\pm$ 0.34, $p < 0.001$). In addition to physiological and hemodynamic differences between the carotid artery and the aorta, HRPF, PA and exercise may have a varied impact on the function along the arterial tree. Regarding IMT, all included studies that measured the vascular structure used an ultrasound device. However, both the type of ultrasound device and the analysis method used, e.g. B-Mode imaging or radiofrequency multiple M-line analysis, influence the magnitude of IMT and, therefore, limit the comparability of the included studies. Thus, only one technique should be performed in prospective studies (67). Following Skilton et al. (68), the choice of location of IMT measurement—at the carotid artery or the aorta—should be decided depending on the target group and the individual goal of each study.

Likewise, we are unable to comment on the role of exercise in young athletes given the limited numer of studies on this subject. As athletes are of special interest with respect to cardiovascular adaptation to exercise, this target population should be the subject of further investigation focused on the duration and intensity of exercise and its impact on vascular structure and function (69).

Future studies are also needed to address the question of wether IMT:diameter-ratio or wall:lumen-ratio and the role of this parameters determining vascular patency. At this time, most studies evaluate only IMT, a parameter that provides a quantitative assessment of wall thickness but does not take into account any changes in the vessel diameter or lumen in response to HRPF, PA and/or specific exercise interventions. Finally, our findings suggest that individual exercise participation should be evaluated quantitatively because intensity and duration likely influence the effectiveness of these interventions.

AUTHOR CONTRIBUTIONS

LB conceptualized the study, reviewed the literature, and drafted the manuscript. HW, RO-F, and TS conceptualized the study and provided important input for drafting and revising of the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

3.2 Article 2

Authors: Lisa Baumgartner, Thorsten Schulz, Renate Oberhoffer, Heidi Weberruß

Title: Influence of Vigorous Physical Activity on Structure and Function of the Cardiovascular System in Young Athletes – the MuCAYA-Study

Journal: Frontiers in Cardiovascular Medicine

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Summary:

This article describes the study protocol of the Munich Cardiovascular Adaptation in Young Athletes Study (MuCAYA study). The study is based on the scientific terms ‘athlete's heart’ and ‘athlete's artery’, which describe adapting the heart and vascular system to intensive training loads. Cardiac adaptation to exercise can be observed, for example, as increased left and right ventricle, increased left ventricular wall thickness, or increased stroke volume. The vascular adaptation is shown by an increase in the diameter or lumen and a reduction in the vascular wall thickness. As the evidence for the interplay of cardiac and vascular adaptation in young athletes needs to be discovered, the MuCAYA study aims to investigate the relationship between the structural and functional parameters of the myocardium and the vessels of young athletes. In addition, the role of training stimuli (type, duration, intensity), muscle strength, and cardiopulmonary fitness will be investigated separately for cardiac and vascular adaptation parameters. The target group is young athletes aged 7 to 18 years who do not have an acute infection or orthopedic injury and get medical approval for cardiopulmonary exercise. The parameters of carotid structural adaptation are cIMT, carotid diameter, and cIDR. The parameters of carotid functional adaptation are AC, Ep, β, and PWVβ. The parameters of the central function adaptation are cSBP and aPWV. End-diastolic left ventricular diameter, left ventricular diastolic posterior wall thickness, diastolic septal thickness, ejection fraction, and shortening fraction are the parameters of cardiac adaptation. The MoMo-AFB records the type, duration, and intensity of physical activity in the settings of school, everyday life, sports clubs, and recreational sports. Muscle strength is assessed with a hand dynamometer, and cardiopulmonary fitness with exercise testing on a bicycle ergometer using a ramp protocol. In addition, a detailed personal and family history is collected, and the blood is examined for inflammatory parameters, for example. The statistical sample size calculation revealed a required number of 252 young athletes. The study is supported by the German Heart Foundation/German Foundation of Heart Research, project number F/06/18.

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Lisa Baumgartner and Heidi Weberruß were the principal investigators of this article. Lisa Baumgartner, Heidi Weberruß, Thorsten Schulz, and Renate Oberhoffer-Fritz designed the study and engaged in acquiring the funding. Lisa Baumgartner and Heidi Weberruß wrote the manuscript. All authors revised the manuscript and approved the final version.

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Influence of Vigorous Physical Activity on Structure and Function of the Cardiovascular System in Young Athletes—The MuCAYA-Study

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Objective: Moderate physical activity (PA) is associated with a reduced risk to develop cardiovascular disease. However, junior athletes exercise between 10 and 20 h a week with intensities exceeding moderate levels by far. In this regard, the cardiovascular system has to increase its work five to six times compared to moderate intensities. This may result in potentially pathological adaptations of the cardiovascular system. The underlying process of vascular adaptations to exercise is yet not fully understood and hardly investigated in junior athletes. An increased blood pressure and pulse wave velocity, ventricular hypertrophy, arrhythmia, and even sudden cardiac death (SCD) has been reported in adult athletes. Studies, examining the cardiovascular system in children, its association to intensity and type of exercise, are rare. Therefore, we present the study protocol of a prospective cross-sectional study that investigates the influence of PA on the cardiovascular system in young athletes.

Methods and Design: Children and adolescents, 7–18 years, presenting for their annual pre-participation screening at the Institute of Preventive Pediatrics, Faculty of Sports and Health Sciences, Technical University of Munich (TUM), are examined in this prospective cross-sectional study. Vascular parameters measured by ultrasound are carotid intima-media thickness (cIMT), vascular stiffness (AC, Ep, β, PWV β), and the vascular diameter (D) to calculate the IMT:Diameter-Ratio (IDR). Cardiac function is evaluated by a 12-lead ECG, and echocardiographic parameters (end-diastolic left ventricular diameter, left ventricular diastolic posterior wall thickness, diastolic septal thickness, left ventricular mass and relative wall thickness, ejection fraction, and shortening fraction). A cardiopulmonary exercise test is performed on a bicycle ergometer, muscular strength is assessed with the handgrip test, and physical activity with the MoMo questionnaire.

Discussion: It is essential to follow young athletes over the course of their career in order to detect pathophysiological changes in the myocardium as soon as possible. If these changes are preceded or followed by changes in vascular structure and function is not known yet. Therefore, we present the study protocol of the Munich Cardiovascular adaptations in young athletes study (MuCAYA-Study) which investigates the association between vascular and cardiac adaptation to intensive exercise in junior athletes.

Keywords: intima-media thickness, vascular stiffness, junior athletes, vascular adaptation, athlete's artery

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BACKGROUND

There is no doubt about positive effects of physical activity (PA) on the human body. Physically active persons reduce their risk of developing type 2 diabetes mellitus, hypertension, and cardiovascular disease (1). Prevalence of atherosclerosis is reduced as well as mortality of cardiovascular disease (2–7). Studies that describe positive effects of physical fitness focus on moderate exercise intensity in children and adults (7). According to WHO recommendations on physical activity (8) children should exercise 60 min at moderate intensity per day with short bouts of anaerobic intensities. Exercises to strengthen muscles and bones should be performed three times a week (8). However, young competitive athletes train between 10 and 20 h per week with intensities exceeding WHO recommendations by far (9). In this regard, the cardiovascular system has to increase its work five to six times, compared to moderate intensity levels (7), which potentially leads to adverse adaptations of the cardiovascular system.

The term "athlete's heart" describes a non-pathological electrophysiological, structural, and functional myocardial adaptation in response to continuous training stimuli in adults. Athletes present 10–15% increased left and right ventricles and a 10–20% increased left ventricular wall thickness. Functionally, an increased stroke volume and improved cardiac filling in diastole, improved capillary conductivity, and oxidative capacity of the skeletal muscle can be observed in athletes (7). Myocardiac cells adapt to regular PA according to the underlying stimulus (endurance or strength training). Endurance activities like long distance running or swimming reduce peripheral vascular resistance and systolic blood pressure (SBP), and increase cardiac stroke volume and output. As a result, myocardial oxygen consumption is reduced. Strength training increases myocardial oxygen consumption, heart rate, blood pressure, peripheral resistance, and stroke volume to a smaller extent (10).

Contrary to positive effects of PA, maladaptations of the cardiovascular system may occur, sudden cardiac death (SCD) is the most severe one (7, 11, 12). In 46 endurance athletes, mean age of 31 years, 18 cases of severe cardiac arrhythmia and 9 cases of SCD were described (13). The MARC study (Measuring Athlete's Risk of Cardiovascular Events) identified coronary sclerosis using cardio CT in almost 19% of athletes (>45 years) who had been asymptomatic, had a low cardiovascular risk profile according to the Systematic Coronary Risk Evaluation (SCORE) and an asymptomatic stress ECG (14).

Characteristic myocardial adaptations to intensive exercise training such as bradycardia, early repolarization, atrial dilatation, and ventricular hypertrophy are also seen in young athletes (15). In an American long-term survey, 1,866 cases of SCD or cardiac arrest were reported in the period between 1980 and 2006 (16). In 56% SCD was caused by cardiovascular disease with hypertrophic cardiomyopathy (HOCM) as predominant diagnosis (36%) (16). In competitive athletes (12–17 years), SCD incidence was highest with 1.17 cases per 100 000 athletes per year (17) with male athletes bearing double the risk than female athletes (18). Regarding these results, it is of high importance to follow young athletes over the course of their career to detect pathophysiological changes in the myocardium as soon as possible (19).

In addition to cardiac adaptations to PA, there is evidence that PA also has an influence on the vascular system. Green, Spence, Rowley, Thijssen and Naylor (20) postulate the concept of an "athlete's artery." They hypothesize that persistently increased PA leads to an increase in diameter and reduction in wall thickness. Heffernan (21) suggests that this vascular remodeling is due to previous cardiac remodeling and triggered by high training intensities. They describe the following cycle: persistently increased cardiac output leads to an adverse effect on the endothelium, an increase in vascular stiffness and consequently end-organ damage of the heart. Hereby SCD risk is increased dramatically.

In young, normally active adults, Boreham et al. (22) found an inverse relationship between arterial vascular stiffness and cardiorespiratory fitness pointing toward reduced stiffness measures in athletes with higher maximum oxygen uptake (VO_{2max}, $r = -0.21$, $p < 0.001$) and PA. Denham et al. (12) report lower vascular stiffness in moderately active men ($r = -0.62$, $p < 0.001$). In contrast, among competitive athletes, exercising at very high intensities, and control persons, negative adaptations to increased training intensities were found. Vlachopoulos et al. (23) report significantly higher blood pressure values and higher pulse wave velocity (PWV) in marathon runners (SBP 113 ± 15 mmHg vs. 102 ± 11 mmHg, diastolic blood pressure, DBP 79 ± 10 mmHg vs. 72 ± 9 mmHg, $p < 0.001$, and PWV 6.89 m/s vs. 6.33 m/s, $p < 0.01$). Abergel et al. (24) showed a 13% higher intima-media thickness (IMT) for professional road cyclists. Schmidt-Trucksäss et al. (25) observed an increased IMT of the femoral artery in endurance and strength-trained athletes. All results refer to comparisons with a control group.

In children, cIMT (carotid IMT) and arterial stiffness are inversely correlated with cardiorespiratory fitness and physical activity (26–29). In contrast to these positive adaptations, Kim et al. (30) observed higher vascular stiffness in young adult American football players. Feairheller et al. (31) report a higher carotid IMT and larger diameter of the brachial artery. In youth, there are no studies examining possible adaptation mechanisms caused by intensive exercise training. Furthermore, the influence of different training stimuli (type of sport, training frequency, and intensity) on the cardiovascular system has not been sufficiently investigated.

Abbreviations: AC, arterial compliance; AEPC, Association for European Paediatric and Congenital Cardiology; cIMT, carotid intima-media thickness; CPET, cardiopulmonary exercise testing; D, vascular diameter; DBP, diastolic blood pressure; Ep, elastic modulus; GLS, global longitudinal strain; HOCM, hypertrophic cardiomyopathy; IDR, IMT:Diameter-Ratio; IMT, intima media thickness; MARC study, Measuring Athlete's Risk of Cardiovascular Events; MuCAYA-Study, Munich Cardiovascular Adaptation in Young Athletes Study; PA, Physical activity; PEH, post exercise hypotension; PWV, pulse wave velocity; PWV β, pulse wave velocity β; SBP, systolic blood pressure; SCD, sudden cardiac death; SCORE, Systematic Coronary Risk Evaluation; TUM, Technical University of Munich; VO_{2max}, maximum oxygen uptake; β, stiffness index β.

In summary, there is no consensus on the effect of intensive exercise on the vascular system. Studies show an influence of aerobic endurance training to vascular properties (20, 32, 33). However, the concept of the "athlete's artery" is not yet completely understood and only examined to a small extent.

Therefore, this prospective cross-sectional study investigates the influence of PA on the cardiovascular system in young athletes. For this purpose, the structure and function of the vascular system and myocardium are examined as well as the association to intensive exercise training. Confounding variables are types of PA (endurance, muscular endurance, strength), cardiopulmonary fitness, muscular strength, and training stimuli (frequency and intensity).

METHODS

Design and Participants

Children and adolescents, 7–18 years, presenting for their annual pre-participation screening, are enrolled in this prospective cross-sectional study over the course of two years. Each year, approximately $n = 250$ children and adolescents are examined at the Institute of Preventive Pediatrics, Faculty of Sports and Health Sciences, Technical University of Munich (TUM).

The following inclusion criteria are applied:

- Age 7–18 years.
- Informed consent by children and/or legal guardians.
- No acute infection.
- No acute orthopedic injury.
- Medical clearance for cardiopulmonary exercise testing.

The study is in compliance with the Declaration of Helsinki and is approved by the TUM ethics committee (project number: 301/18 S). Informed consent is contained of all children and/or their legal guardians.

Measurements

Parameters of Vascular Adaptation

cIMT as structural vessel parameter is measured after 10–15 min rest in supine position at the far wall of the common carotid artery with the head turned 45° opposite to the site being investigated. cIMT is examined 1 cm proximal to the bifurcation at the end of diastole at two angles on the right side (120°/150°) and two angles on the left side (210°/240°). Measurements are performed in B-mode ultrasound according to the guidelines of the Association for European Paediatric and Congenital Cardiology (AEPC) (34). Using the eTracking method (ET, M-mode), vascular stiffness, and common carotid artery diameter is measured in the same position, two times on the right and two times on the left side (150°/210°). Parameters of vascular stiffness are arterial compliance (AC), elastic modulus (Ep), stiffness index β (β), and local pulse wave velocity (PWV β), according to following formula (35):

$$AC = \pi \frac{(D_{max^2} - D_{min^2})}{4\,(BP_{max} - BP_{min})}$$

$$Ep = \frac{BP_{max} - BP_{min}}{\frac{D_{max} - D_{min}}{D_{min}}}$$

$$\beta = \frac{ln\frac{BP_{max}}{BP_{min}}}{\frac{D_{max} - D_{min}}{D_{min}}}$$

$$PWV\beta = \sqrt{\frac{\beta^{*} BP_{min}}{2\rho}}$$

Vascular diameter (D) is measured at diastole, to calculate IMT:Diameter-Ratio (IDR) as parameter of functional adaptation (eccentric vs. concentric hypertrophy) of the vessel wall (36). cIMT and distensibility parameters of young competitive athletes will be compared to healthy controls (37). All measurements are performed with the ProSound Alpha 7 ultrasound system (Hitachi Medical Systems GmbH, Wiesbaden, Germany).

Parameters of Cardiac Adaptation

End-diastolic left ventricular diameter, left ventricular diastolic posterior wall thickness, and diastolic septal thickness are well-established parameters to describe myocardial morphology. They are examined via ultrasound (GE VIVID 7 Dimension ultrasound system and GE ECHOPAD software, GE Healthcare, Horten, Norway) in a resting position with slightly lateral inclination by two-dimensional M-mode. Structural parameters are compared to reference values of Pettersen et al. (38). Left ventricular mass is calculated according to Devereux and Reichek (39) and left ventricular relative wall thickness according to Lang et al. (40). Functional parameters are ejection fraction and shortening fraction.

Physical Activity

The MoMo activity questionnaire is a comprehensive questionnaire that records PA in different settings: school, everyday activity, PA organized in a club and leisure time PA outside a club (41). All activities are defined by frequency and/or duration and intensity. Minutes of exercise per week and metabolic equivalent (MET) minutes per week are calculated for each item, which allows calculation of an overall activity-index. One MET refers to the amount of oxygen (O_2) the body consumes sitting at rest. It equals 3.5 ml O_2 per kg body mass per minute (42). Additionally, overall PA is calculated according to Prochaska et al. (43) with the distinction on meeting the WHO-Guideline (8) or not.

Muscular Strength

The hand grip test is applied to assess childrens' strength and the influence of strength on cardiovascular adaptation. In a seated position with upright upper body, shoulders adducted, and elbow flexed in 90°, participants push the hand grip dynamometer (SAEHAN Hydraulic Hand Dynamometer SH5001, SAEHAN Corporation, Masan, South Korea) at maximum strength, three times with the right and left hand, respectively (44).

Cardiovascular Basic Diagnostics

All participants undergo a 12-channel ECG at rest (CARDIOVIT CS-200 Office, SCHILLER AG, Baar, Switzerland). Peripheral and central SBP and DBP, peripheral and central pulse pressure (PP), and aortic PWV are measured after a 5-min resting period using the Mobil-O-Graph (Mobil-O-Graph, IEM, Stolberg, Germany).

The cuff (size according to upper arm circumference) is placed on the left arm.

Cardiopulmonary Fitness

VO_{2max} is determined by cardiopulmonary exercise testing (CPET, ramp protocol; Ergostik, Geratherm Respiratory GmbH, Bad Kissingen, Germany) on a bicycle ergometer (Lode Corival, Lode BV, Groningen, The Netherlands) plus 12 lead ECG. Relative maximum load (W/kg) and relative VO_{2max} (ml O_2/min/kg) are calculated to determine participants' exercise capacity. Ventilation thresholds (VT1 and VT2) are defined by the V-slope method (45).

Personal and Family History

The personal history includes past and present illnesses and injuries, vaccination status, alcohol consumption, smoking cigarettes, drug use, psychological status, as well as girls' menarche, menstruation cycle and HPV vaccine. Family history includes past and current occurrence of cardiovascular disease, SCD, unclear death, metabolism disorders, diabetes mellitus, psychiatric disorders, malignancies, and presence of Marfan syndrome. In addition, exercise-related symptoms, such as dyspnoea, dizziness/syncope, palpitations or pain, are inquired.

Laboratory Chemical Analysis

Venous blood samples include the following parameters: hemoglobin, erythrocytes, hematocrit, MCV, MCH, MCHC, erythrocyte distribution, platelets, leukocytes, creatinine, GPT, GOT, uric acid, cholesterol, and CRP, to exclude infections, inflammatory diseases or anemia or increased blood lipid levels.

Sample Size Calculation

A sample of $n = 252$ athletes is needed per year to detect a mean difference in cIMT of 0.05 mm, given a confidence interval of 95% and statistical power of 80%. The variation in this population is 0.04 mm. The difference in cIMT of 0.05 mm indicates the difference between median cIMT (0.46 mm) defined at the 50th percentile and an abnormal increased cIMT (0.51 mm) above the 95th percentile.

Statistical Analyzes

Differences between structural and functional parameters of the cardiovascular system will be compared to age- and sex-specific reference values (37–39). Linear regression analyses are performed to investigate the association between VO_{2max} and training stimuli (frequency, intensity) to changes of the cardiovascular system and to analyze a correlation between arterial and myocardial adaptations, relative to the type of exercise (frequency, intensity). Dependent parameters are arterial structure and function as well as myocardial structure and function. Independent parameters are VO_{2max} and METs per week. Results are controlled for age, sex, BMI, BP, dietary behavior, blood cholesterol levels, and smoking.

DISCUSSION

This study aims to investigate the effect of PA on vascular and cardiac structure and function in young athletes. Furthermore, the influence of different types of PA (endurance, muscular endurance, strength), cardiopulmonary fitness, and training stimuli (frequency, intensity) on arterial structure and function are investigated, as well as the correlation of arterial structure and function to the structure and function of the heart.

Cardiac Adaptation to PA

Cardiac remodeling is the process of changes of the myocardium. It is caused by hemodynamic pressure and volume loads (increased heart rate and ejection fraction, and increased blood pressure) and by biochemical mediators such as endothelin, cytokines, nitrogen, and oxidative stress by radical oxygen species (46). Hemodynamic influences stimulate cardiomyocytes to increase the expression of sarcomeres. Several studies have shown cardiac adaptations to PA in adult athletes (24, 47–50). Sharma et al. (7) consider too intensive exercise training as multifactorial risk factor in the course of an athlete's life that only becomes symptomatic in adulthood. The authors mentioned a higher risk to develop dilated cardiomyopathy in athletes with an enlarged left ventricle and lower ejection fraction. Makan et al. (51) compared 900 adolescent athletes (15.7 ± 1.2 years, endurance, kickback, and team sports) with 250 healthy controls. They showed an enlargement of the left ventricle in 18% of athletes (>54 mm) with normal systolic and diastolic function. Sharma et al. (19) studied the wall thickness of the left ventricle within the same collective ($n = 720$ athletes) and found an increased wall thickness in athletes compared to controls (9.5 ± 1.7 mm vs. 8.4 ± 1.4 mm, $p < 0.01$). In addition, 5% of participants had abnormal wall thickness values and showed an enlarged left ventricle (54.4 ± 2.1 mm). As highest values were observed in rowers, authors assumed a combination of intensive isometric and isotonic exercise that triggers hypertrophy of the left ventricle (19). In both studies, authors hypothesize an initially physiological adaptation of the myocardium that converts into a pathological adaptation.

The cardiovascular system is very sensitive to mechanical stimuli, such as an increased heart rate, increased ventricular filling, and increased arterial shear stress. This can also lead to adverse adaptations (52). In general, endurance training is considered to bear a positive effect on the myocardium. Strength training, on the contrary, has a potentially negative effect due to excessive pressure loads (53, 54). Heidbuchel et al. (13) do not differentiate between endurance and strength training, but consider intensive training bouts and/or recovery periods between training sessions that are too short, as one potential explanation for negative adaptations of the cardiovascular system. Adequate exercise training with an appropriate recovery time, on the other hand, may lead to a positive adaptation of the cardiovascular structure and function (55).

Vascular Adaptation to PA

Green et al. (20) suspect increased blood pressure levels as trigger for changes in vascular structure and function. These changes are responsible for functional physiological as well as pathological processes. Bertovic et al. (32) observed increased vascular stiffness caused by blood pressure peaks during strength training. As stimulus, they consider a change in the proportion of smooth muscle cells in the intima layer and a relative increase in the ratio of collagen to elastin in the media layer. As intensive endurance exercise also causes peaks in blood pressure, this could be a possible trigger for pathological adaptations of the vascular structure, too.

Increased inflammatory markers after intensive exercise could also have an impact on blood vessels. Increased leukocytes and CRP were found in athletes after a marathon race and associated with an increase in vascular stiffness (20, 56, 57). Sharma et al. (7) refer to the relationship between increased arterial shear stress and increased oxidative stress, which may cause the development of atherosclerosis. The consequence of atherosclerotic changes is, inter alia, increased vascular resistance with subsequently higher myocardial oxygen consumption. The consequence of increased vascular stiffness is an increased ventricular afterload, which leads to left ventricular hypertrophy and decreased cardiac perfusion during diastole (58). Whether the increased vascular stiffness causes cardiac changes or if increased vascular stiffness is the result of previous myocardiac adaptations has not yet been investigated.

Positive adaptations due to exercise can be induced by increased shear stress and the associated release of vasoactive substances such as NO (12, 20, 26, 59). Furthermore, moderate endurance exercise stimulates endothelial progenitor cells that positively influence endothelial function (59–61). Moderate aerobic endurance exercise has a positive effect on blood pressure levels and is recommended as non-pharmacological therapy to treat arterial hypertension (62). Vasodilating agents that are released during exercise are only slowly reduced at the end of moderate exercise. They result in low blood pressure levels (63, 64). The mechanism of this effect, called post-exercise hypotension (PEH), can last up to 10 h, with positive effects (increased elasticity or decreased rigidity) on the vascular system (65, 66).

In general, functional and structural changes are less pronounced in adolescent athletes due to their younger training history than in adults (19, 51). At this age, pathophysiological changes could still be counteracted and therefore prevented by adequate training control.

Interaction of Cardiac and Vascular Adaptation to PA

In line with the definition of the athlete's heart, it is questionable in which way the vascular system adapts to training loads and whether there is a physiological relationship between cardiac and vascular adaptation (20, 67). Bell et al. (68) report an association between femoral artery stiffness and Global Longitudinal Strain (GLS) in adults without cardiovascular disease in the Framingham Heart Study—the higher the vessel stiffness, the higher and thus the worse was GLS. Based on the literature, this effect is intensified by intensive exercise. The association between vascular and cardiac adaptations to PA in youth has not been fully studied. In addition, it is unclear whether the known adaptation phenomena of the myocardium precedes an adaptation of the vascular system or whether the vascular system subsequently adapts to changes of the myocardium.

Several studies demonstrate a U- or J-shaped curve of PA and health. Initially, physical activity is positively associated with better health status up to the vertex, which reflects the turning point with higher risk for cardiovascular events underneath and above a healthy threshold of PA in adults (69–71). The question therefore arises, whether this negative effect of exceptionally high volume of PA manifests itself in youth. In addition, it may therefore be possible that prolonged and intensive PA impairs vascular health in young athletes. In this context, pathophysiological reactions as result of intensive PA should be investigated in relation to the type, intensity, and duration of PA.

LIMITATIONS

This study is a first step towards an analysis of cardiac and vascular structure and function in junior athletes. It will provide cross-sectional data as basic research for future longitudinal studies. The age-range covered is from 7 to 18 years and includes participants within different levels of their physiological, neurological, and mental development. It covers the age-range before, during, and after puberty which has an impact on hormonal status and thus on physical components. To account for this differences, participants will be compared to age- and sex-specific reference values and within their age-groups.

We collect data on participants' training history to account for the time span they've been involved in competitive sports, to differentiate between shorter and longer exposure to physical training. What we cannot account for with this data is how participants respond to physical stimuli, as there will be athletes being predominantly disposed to muscular and cardiovascular adaptation than others. Genetic factors are not involved in the study at this point but could be one major aspect of future work as well as more laboratory parameters. Family history is assessed in the medical interview and will be reviewed for a history of cardiac disease or other health issues. This part could also be extended toward a family training history.

CONCLUSION

The positive influence of physical activity on the cardiovascular system is affected by negative adaptations of intensive training stimuli and years of intensive endurance exercise in adults. This is reflected by changes in myocardial morphology and myocardial function as well as vascular structure and vascular function. In young athletes, increased wall thickness and increased lumen of the left ventricle were observed. Studies investigating the influence of intensive physical activity on the structure and function of the vascular system in young athletes do not yet exist. In children and adolescents studies show an association between moderate physical activity and positively altered structural and functional vascular parameters - however, these studies refer to athletes with normal levels of activity (according to the WHO recommendation). The role of type of sport, exercise frequency, and exercise intensity in the adaptation process is still unclear in adults and young athletes. Additionally, the long-term effects of this adaptation have not been sufficiently investigated (20, 72). This raises the question whether there is too much exercise from a cardiovascular point of view and whether a relationship between vascular function and vascular structure as well as myocardial function and myocardial morphology can be observed in young athletes.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee of the Technical University of Munich (project number: 301/18 S). Written informed consent to participate in this study was provided by the participants and/or legal guardian.

AUTHOR CONTRIBUTIONS

LB and HW were involved in study conception and drafting the manuscript. TS and RO were involved in study conception and critically reviewed the manuscript. All authors have read and approved the final version of this manuscript.

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3.3 Article 3

Authors: Lisa Baumgartner, Heidi Weberruß, Katharina Appel, Tobias Engl, Daniel Goeder, Renate Oberhoffer-Fritz, Thorsten Schulz

Title: Improved Carotid Elasticity but Altered Central Hemodynamics and Carotid Structure in Young Athletes

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Summary:

For adult athletes, there is already broad evidence that they have alterations in arterial wall thickness, lumen, and elasticity. In contrast, the group of youth athletes has been studied only sporadically concerning their vascular properties. The study aimed to describe the carotid structure, elasticity, stiffness, and central arterial stiffness of young athletes aged between 12 and 17 years who are active in sports clubs for at least 6 hours per week (training and competition) and to investigate differences between male and female young athletes. The results of central hemodynamics were compared with age- and sex-specific reference values of Elmenhorst et al. (135) and the results of carotid structure and function with age- and sex-specific reference values of Weberruß et al. (138) and Semmler et al. (139). This article includes the first examination of a subsample of 331 children and adolescents from 27 different types of sports who completed pre-participation screening between November 2017 and September 2020 and had no cardiovascular or metabolic disease or acute infection at the time of the examination. Noninvasive ultrasound was performed in all young athletes to determine the carotid structure (cIMT, carotid diameter, cIDR) and function (AC, β, Ep, PWVβ) using the ultrasound device ProSound Alpha 7 (Aloka/ Hitachi Medical Systems GmbH, Wiesbaden, Germany). In addition, peripheral and central blood pressure and aPWV were recorded using Mobil-O-Graph®. For statistical analysis, raw scores were converted to standard deviation scores (SDS) and analyzed using a one-sample t-test. The central finding of this study is that young athletes had significantly higher cIMT (cIMT SDS: 0.37 ± 1.34, $p < 0.001$) and cIDR (cIDR SDS: 0.20 ± 1.41, $p = 0.009$), but simultaneously better carotid elasticity (AC SDS: 0.99 ± 0.83, $p < 0.001$) and lower carotid stiffness (β SDS: −0.75 ± 0.88, $p < 0.001$; Ep SDS: −0.88 ± 0.93, $p < 0.001$; PWVβ SDS: −1.04 ± 0.97, $p < 0.001$) compared with appropriate reference values. In contrast, central arterial stiffness (cSBP SDS: (0.42 ± 1.29, $p < 0.001$; aPWV SDS: 0.55 ± 1.33, $p < 0.001$) was increased. In total, 40.8% had cIMT > 75^{th} percentile. Boys

showed significantly higher cIMT (0.49 ± 0.04 mm vs. 0.47 ± 0.04 mm, $p < 0.001$), carotid diameter (5.68 ± 0.46 mm vs. 5.56 ± 0.40 mm, $p = 0.034$), and central arterial stiffness (cSBP: 107.4 ± 10.4 mmHg vs. 103.3 ± 7.92 mmHg, $p < 0.001$; aPWV: 5.02 ± 0.44 m/s vs. 4.79 ± 0.32 m/s, $p < 0.001$) compared to girls. In the collective of young athletes with high exercise capacity, the high proportion of young athletes with thickened cIMT, altered cIDR, and increased central arterial stiffness was not expected. Considering the improved carotid elasticity and reduced carotid stiffness, the results suggest a functional adaptation of the CCA to exercise. A possible explanation could be proliferation of VSMC in the tunica media and improved vascular reactivity. The carotid structure should be further observed in longitudinal studies along with central arterial stiffness. In addition, vascular properties should be assessed in interaction with cardiac structure and function to determine the overall cardiovascular adaptation to exercise in young athletes.

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Individual contribution:

Lisa Baumgartner was the principal investigator of this article. Lisa Baumgartner, Heidi Weberruß, Thorsten Schulz, and Renate Oberhoffer-Fritz designed the study and engaged in acquiring the funding. Lisa Baumgartner (ultrasound, Mobil-O-Graph®, MoMo-AFB), Katharina Appel (spiroergometry), Tobias Engl (Mobil-O-Graph®), and Daniel Goeder (spiroergometry) collected the data. Lisa Baumgartner analyzed the data and wrote the manuscript. All authors revised the manuscript and approved the final version.

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Improved Carotid Elasticity but Altered Central Hemodynamics and Carotid Structure in Young Athletes

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Young athletes most often exceed the physical activity recommendations of the World Health Organization. Therefore, they are of special interest for investigating cardiovascular adaptions to exercise. This study aimed to examine the arterial structure and function of young athletes 12–17 years old and compare these parameters to reference values of healthy cohorts. Carotid intima-media thickness (cIMT), carotid diameter, cIMT÷carotid diameter-ratio (cIDR), arterial compliance (AC), elastic modulus (Ep), β stiffness index (β), and carotid pulse wave velocity (PWVβ) were determined using ultrasound in 331 young athletes (77 girls; mean age, 14.6 ± 1.30 years). Central systolic blood pressure (cSBP) and aortic PWV (aPWV) were measured using the oscillometric device Mobil-O-Graph. Standard deviation scores (SDS) of all parameters were calculated according to German reference values. The 75th and 90th percentiles were defined as the threshold for elevated cIMT and arterial stiffness, respectively. Activity behavior was assessed with the MoMo physical activity questionnaire, and maximum power output with a standard cardiopulmonary exercise test. One-sample *t*-tests were performed to investigate the significant deviations in SDS values compared to the value "0". All subjects participated in competitive sports for at least 6 h per week (565.6 ± 206.0 min/week). Of the 331 young athletes, 135 (40.2%) had cIMT >75th percentile, 71 (21.5%) had cSBP >90th percentile, and 94 (28.4%) had aPWV >90th percentile. We observed higher cIMT SDS ($p < 0.001$), cIDR SDS ($p = 0.009$), and AC SDS ($p < 0.001$) but lower β SDS ($p < 0.001$), Ep SDS ($p < 0.001$), and PWVβ SDS ($p < 0.001$) compared to the reference cohort. The cSBP SDS ($p < 0.001$) and aPWV SDS ($p < 0.001$) were elevated. In conclusion, cIMT and cIDR were higher in young athletes than in a reference cohort. Furthermore, young athletes presented better carotid elasticity and lower arterial stiffness of the carotid artery. However, central arterial stiffness was higher compared to the reference cohort. The thickening of the carotid intima-media complex in combination with a reduction in arterial stiffness indicates a physiological adaptation to exercise in youth.

Keywords: arterial stiffness, arterial elasticity, carotid intima-media thickness, young athletes, exercise

INTRODUCTION

Regular physical activity reduces the risk of mortality and the incidence of cardiovascular disease worldwide (Lear and Yusuf, 2017). In youth, being active is associated with normal blood pressure (BP) and normal weight status (Leary et al., 2008). On the other hand, inactivity in youth is associated with elevated BP, which predicts hypertension in adulthood (Chen and Wang, 2008; Leary et al., 2008). Furthermore, inactivity increases the risk of being overweight or obese, which is also associated with hypertension (Chen and Wang, 2008; Juhola et al., 2011). Overweight or obese children and adolescents are more likely to be overweight or obese as adults (Singh et al., 2008; Juhola et al., 2011). The promotion of a healthy lifestyle is important in avoiding adverse effects and strengthening health resources. Therefore, the World Health Organization (WHO) recommends moderate to vigorous physical activity of at least 60 min per day in children and adolescents (World Health Organization, 2020).

The Windkessel function explains the way elastic arteries convert the pulsating blood ejections from the heart into a steady blood flow. Elastic arteries passively expand due to the BP and temporarily store some blood volume. During diastole, elastic arteries retract, thereby pushing the stored blood volume along the arterial tree. With increasing arterial stiffness, the heart has to work harder to overcome higher pressure in the vasculature. Thus, long-term increases in arterial stiffness can lead to left ventricular (LV) hypertrophy and LV failure (Luft, 2012). Arterial wall thickness and arterial compliance within the normal range are indicators of vascular health. Within the intima-media complex of the arterial wall, the tunica media is the thickest layer of arteries and consists of vascular smooth muscle cells (VSMC), collagen, and elastin (Paneni, 2017). VSMC regulate contraction of the artery and the elastic recoil of arteries in different hemodynamic situations (Basatemur et al., 2019). The tunica intima consists of the endothelium and basement membrane. The thickening of the intimal layer is a preliminary stage of atherosclerosis (Insull, 2009). This stage is characterized by the clonality of VSMC in the intimal layer, whereby VSMC seem to originate from the medial layer (Kaur et al., 2017; Basatemur et al., 2019).

Physical activity leads to a physiological process because it increases blood flow and, therefore, enhances shear stress. The increased shear stress induces prostacyclin release and endothelial nitric oxide synthase (eNOS) activity leading to increased NO production. NO inhibits the release of the vasoconstrictor, endothelin, resulting in exercise-induced vasodilation and, thus, improved vascular function. Physical activity also improves the morphometry of conduit arteries; arterial diameter increases, the dilating capacity is improved, and wall thickness is reduced (Green et al., 2017). Therefore, regular physical activity and exercise are effective primary and secondary prevention strategies to reduce arterial wall thickness and arterial stiffness, especially in at-risk populations e.g., overweight and obese patients (Baumgartner et al., 2020).

Araújo and Scharhag (2016) defined young athletes as between 12 and 17 years old, who practice exercise training to improve their performance, participate in sports competitions, are registered in sports federations, and practice their sport as a major way of living. Young athletes most often exceed the WHO physical activity recommendations and, therefore, are of special interest for investigating cardiovascular adaptions to exercise (Sharma et al., 2002). Bjerring et al. (2018) investigated 76 pre-adolescent cross-country skiers and found increased LV end-diastolic volume, LV mass, right ventricular (RV) basal diameter, and RV area. Furthermore, De Luca et al. (2011) observed higher LV diastolic diameter in 50 cyclists, soccer and basketball players with a mean age of 18.5 ± 0.5 years. In addition to cross-sectional studies, D'Ascenzi et al. (2017) found increased RV outflow tract and RV basal end-diastolic diameter in swimmers compared to controls. These data indicate that cardiac adaptation to exercise starts at a young age.

Exercise training strains both cardiac dimensions and vascular properties; evidence shows that athletes have alterations in vascular structures and function. In adults, the concept of an athlete's artery is discussed that postulates an association between endurance activities and reduced arterial wall thickness with a simultaneously enlarged arterial lumen, and better arterial function at all ages (Green et al., 2012, 2017). In contrast, adults performing strength sports seem to have increased arterial wall thickness and enlarged arterial lumen (Feairheller et al., 2016). Aerobic exercise seems to have a greater impact on the stiffness of peripheral (conduit) arteries such as the common carotid artery (CCA) compared to the aorta (Ashor et al., 2014). In normally active children and adolescents, improved endothelial function and arterial wall thickness have been reported (Edwards et al., 2012; Idris et al., 2015).

This study aimed to determine the arterial structure and function of young athletes 12–17 years old and compare these parameters to reference values of a healthy cohort. We hypothesized that young athletes have better vascular properties, defined by lower carotid intima-media thickness (cIMT), increased arterial elasticity, and lower arterial stiffness.

MATERIALS AND METHODS

This prospective study was conducted between November 2017 and September 2020 at our pediatric sports medical outpatient department. All participants and their legal guardians gave written informed consent to participate in this study. The study was approved by the local ethics committee (project numbers 301/18 S and 131/19 S-SR).

Study Subjects

Children and adolescents visited our outpatient department for a pre-participation screening and ultrasound measurement of the CCA. The children and adolescents were enrolled into this study via their regular pre-participation screening. They were not recruited specifically, but voluntarily agreed to the examination in order to receive information about their sports aptitude. Therefore, the inference of our sample to the overall population of young athletes is limited. Of the 733 patients screened, 412 met the following inclusion criteria: age between 12 and 17 years, no acute infection, absence of cardiovascular or metabolic diseases, and participation in a competitive sports club activity for at least

6 h per week in addition to leisure-time physical activities and physical education. Of the 412 young athletes, 81 were measured twice, but only the first examination was included in the analysis. Thus, the final data set was composed of 331 young athletes (77 female, **Figure 1**). The athletes participated in the following sports club activities: soccer ($n = 127$), volleyball ($n = 41$), hockey ($n = 33$), wrestling ($n = 20$), basketball ($n = 17$), handball ($n = 15$), cross-country skiing ($n = 13$), rowing ($n = 13$), swimming ($n = 10$), judo ($n = 6$), track and field ($n = 5$), billiard ($n = 4$), ski jumping ($n = 4$), biathlon ($n = 3$), jiu-jitsu ($n = 3$), skiing ($n = 3$), cycling ($n = 2$), gymnastics ($n = 2$), snowboard ($n = 2$), climbing ($n = 1$), cycle ball ($n = 1$), ice hockey ($n = 1$), running ($n = 1$), sailing ($n = 1$), synchronized swimming ($n = 1$), tennis ($n = 1$), and triathlon ($n = 1$). The study participants were requested that the last food intake should be approximately 1 hour before the examination. In addition, no intensive training should take place 48 h before the examination. None of the young athletes reported smoking.

Brachial Blood Pressure and Central Arterial Stiffness

Brachial systolic (bSBP), diastolic blood pressure (bDBP), and central arterial stiffness were examined with a single measurement using a noninvasive oscillometric device (Mobil-O-Graph®, IEM, Stolberg, Germany). Measurements were taken from the left upper arm in a supine position after 10 min of rest. Cuff size was determined according to the upper arm circumference (XS, 14–20 cm; S, 20–24 cm; M, 24–32 cm; L, 32–38 cm; XL, 38–55 cm). Central systolic blood pressure (cSBP) and aortic pulse wave velocity (aPWV) were calculated indirectly from pulse wave assessed at the brachial artery using the ARCSolver Algorithm (Austrian Institute of Technology, Vienna, Austria) (Wassertheurer et al., 2010). Standard deviation scores (SDS) for bSBP and bDBP were calculated according to the German reference values of Neuhauser et al. (2013). The SDS for cSBP and aPWV were calculated according to the German reference values of Elmenhorst et al. (2015).

Carotid Structure and Function

The cIMT was measured semi-automatically using B-mode ultrasound 1 cm proximal to the bifurcation of the CCA, according to the recommendations of the Association for European Pediatric Cardiology (Dalla Pozza et al., 2015). Patients were positioned in a supine position, with a slightly extended neck and head turned 45° opposite to the side being investigated. After 10 min of rest, four end-diastolic cIMT measurements were taken on the far wall at two angles on the left (210° and 240°) and two angles on the right (120° and 150°) side. Using a three-lead electrocardiogram (ECG), the end-diastolic phase was determined.

Carotid function and diameter were determined using the echo-tracking method in M-mode ultrasound in the same position as the cIMT measurement. Tracking gates, placed at the CCA near and far wall, tracked the wall motion during five consecutive heart cycles. Carotid diameter in systole (D_{max}) and diastole (D_{min}) were measured and parameters for elasticity and stiffness were calculated according to the following formulas:

$$\text{Arterial compliance } (AC) = \pi \frac{(D_{max^2} - D_{min^2})}{4^*(bSBP - bDBP)} \quad (1)$$

$$\text{Elastic modulus } (Ep) = \frac{bSBP - bDBP}{\frac{D_{max} - D_{min}}{D_{min}}} \quad (2)$$

$$\beta \text{ stiffness index } (\beta) = \frac{\ln \frac{bSBP}{bDBP}}{\frac{D_{max} - D_{min}}{D_{min}}} \quad (3)$$

$$\text{Carotid pulse wave velocity } (PWV\beta) = \sqrt{\frac{\beta^* bDBP}{2\rho}} \quad (4)$$

Carotid diastolic diameter was used to calculate the cIMT÷carotid diameter ratio (cIDR). All parameters were calculated as the average of four measurements. SDS were calculated using German reference values, which were assessed with the same protocol and equipment (ProSound Alpha 7 with a linear array of 5–13 MHz, Hitachi Healthcare, Tokyo, Japan) (Weberruß et al., 2015; Semmler et al., 2020).

Physical Activity and Performance

Weekly training duration and intensity were recorded using the MoMo Physical Activity Questionnaire for pupils (Schmidt et al., 2016). All athletes reported the time (min/week) they spent exercising in their sport, the number of months they performed this amount of training for the past year, and the subjective intensity (low, moderate, and high). By multiplying the time and the ratio of the number of months divided by 12, the training duration per week was determined. Depending on the intensity, each type of sport was assigned an individual MET value (Ridley et al., 2008; Ainsworth et al., 2011). To calculate the MET-hours-index, the MET values were multiplied by the training duration and divided by 60. The training experience was assessed based on the number of years the young athletes have practiced their sport on a competitive level.

Physical performance of the young athletes was measured using a standard cardiopulmonary exercise test on an electronically braked cycle ergometer (Lode Excalibur, Lode B.V., Groningen, Netherlands), following international criteria (American College of Sports Medicine, 2014; Massin, 2014). Each young athlete performed a standardized ramp protocol adapted by Godfrey (1974), after a 2-min warm-up period. Ramp inclination was determined by calculating the estimated maximum performance in W/kg (Paridon et al., 2006) and the estimated exhaustion after 10 ± 2 min (Takken et al., 2017). Subjects performed the exercise test at a pedal rate of 70–80 revolutions per minute. Maximum power output was recorded and related to body weight (W/kg). Heart rate was continuously recorded using a 12-lead ECG (CardioPart12, AMEDTEC, Aue, Germany). SDS of maximum power output were calculated using the reference values of Blanchard et al. (2018).

Statistical Analysis

Underweight (<10th percentile), normal weight (10th–90th percentile), overweight (>90th to 95th percentile), and obesity

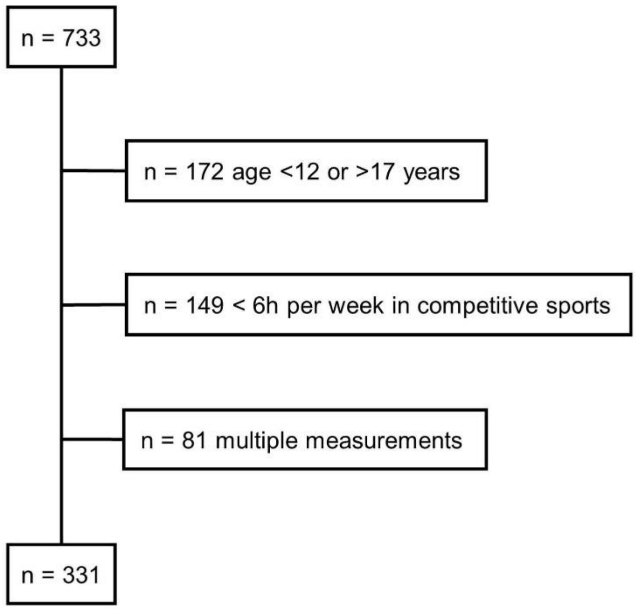

FIGURE 1 | Flowchart of inclusion and exclusion of study subjects.

(>95th percentile) were defined according to age- and sex-specific German reference values (Kromeyer-Hauschild, 2001). Hypertension was determined as BP >95th percentile (Neuhauser et al., 2013). Impaired arterial structure was defined as cIMT or cIDR >75th percentile (Dalla Pozza et al., 2015). Stiffness parameters >90th percentile and AC <10th percentile were defined as elevated arterial stiffness and reduced arterial elasticity, respectively (Elmenhorst et al., 2015; Urbina et al., 2019). A cSBP >90th percentile was defined as elevated cSBP (Elmenhorst et al., 2015).

Descriptive data are expressed as mean value ± standard deviation or in relative values (%). The cIMT, carotid diameter, cIDR, AC, β, Ep, PWVβ, cSBP, and aPWV are presented as raw values and SDS, according to corresponding reference values.

One investigator performed all measurements. Reproducibility of the ultrasound measurement was examined in 20 young adults measuring every individual twice. We used coefficients of variation (CV) to assess the intra-observer variability for the principal investigator and inter-observer variability between the investigator of this study and the reference collective (Weberruß et al., 2015).

After testing for normal distribution, sex differences were analyzed using unpaired Student's *t*-tests. One-sample *t*-tests were performed to investigate the deviations of SDS values compared to the value "0". Since there were missing values for some parameters, we performed an analysis of missing values (oscillometry, ultrasound, and ergometry). Missing values were imputed using fully conditional specification with age, sex, body weight, and body height as predictors only and all variables with missing values as predictors and imputing variables. Data were analyzed using IBM SPSS version 25.0 (SPSS, Inc. Chicago, IL, USA). A p-value of < 0.05 was considered statistically significant.

RESULTS

The mean age of the 331 young athletes (23.3% female) was 14.6 ± 1.30 years. Body mass was 59.1 ± 12.4 kg and body height was 170.7 ± 11.3 cm (**Table 1**). The mean body height SDS was 0.37 ± 1.14 (**Table 2**). 16 subjects (4.8%) were underweight, 15 (4.5%) were overweight, and 2 (0.6%) were obese. Participants exercised 565.6 ± 206.0 min/week in their sport, and the training duration was higher in girls than in boys (619.2 ± 237.6 min/week vs. 546.8 ± 192.7 min/week, $p = 0.007$). The young athletes reported a MET-hours-index of 87.7 ± 33.8. The average training experience was 3.65 ± 2.51 years. Compared to females, male young athletes showed a higher absolute (280.1 ± 65.0 W vs. 232.0 ± 36.9 W, $p < 0.001$) and relative maximum power output (4.68 ± 0.49 W/kg vs. 4.16 ± 0.52 W/kg, $p < 0.001$) in the exercise test. The SDS for maximum power output was 1.85 ± 1.15 (**Table 2**).

Intra- and Inter-Observer Variability

Table 3 shows the intra- and inter-observer variability of ultrasound measurements. Intra-observer variability was lower than inter-observer variability. Both intra- and inter-observer CV were lowest in cIMT (0.58 and 2.09). PWVβ had the lowest intra-

TABLE 1 | Study characteristics.

	Total ($n = 331$)	Boys ($n = 254$)	Girls ($n = 77$)	*p*
	M ± SD	M ± SD	M ± SD	
Age (yrs)	14.6 ± 1.30	14.7 ± 1.31	14.6 ± 1.28	0.556
Body mass (kg)	59.1 ± 12.4	60.0 ± 13.1	56.2 ± 9.12	**0.005**
Body height (cm)	170.7 ± 11.3	172.1 ± 11.8	166.1 ± 8.34	**< 0.001**
BMI (kg/m²)	20.1 ± 2.48	20.0 ± 2.52	20.3 ± 2.32	0.340
BSA (m²)	1.67 ± 0.23	1.69 ± 0.24	1.61 ± 0.16	**0.001**
bSBP (mmHg)	115.7 ± 9.29	116.5 ± 9.51	113.1 ± 8.00	**0.004**
bDBP (mmHg)	65.0 ± 6.20	64.9 ± 6.28	65.5 ± 5.97	0.440
Training duration (min/week)	565.6 ± 206.0	546.8 ± 192.7	619.2 ± 237.6	**0.007**
Training intensity (MET-hours-index)	87.7 ± 33.8	85.8 ± 29.1	94.2 ± 45.9	0.138
Training experience (years)	3.65 ± 2.51	3.70 ± 2.52	3.50 ± 2.48	0.550
Maximum power output (W)	268.9 ± 63.0	280.1 ± 65.0	232.0 ± 36.9	**< 0.001**
Maximum power output (W/kg)	4.56 ± 0.54	4.68 ± 0.49	4.16 ± 0.52	**< 0.001**
cIMT (mm)	0.48 ± 0.04	0.49 ± 0.04	0.47 ± 0.04	**< 0.001**
Carotid diameter (mm)	5.65 ± 0.45	5.68 ± 0.46	5.56 ± 0.40	**0.034**
cIDR (%)	0.09 ± 0.01	0.09 ± 0.01	0.08 ± 0.01	0.174
AC (mm²/kPa)	1.52 ± 0.33	1.53 ± 0.33	1.49 ± 0.35	0.294
β	3.23 ± 0.72	3.23 ± 0.71	3.23 ± 0.73	0.934
Ep (kPa)	37.9 ± 8.70	37.9 ± 8.55	37.8 ± 9.26	0.956
PWVβ (m/s)	3.61 ± 0.37	3.61 ± 0.36	3.63 ± 0.42	0.652
cSPB (mmHg)	106.5 ± 10.1	107.4 ± 10.4	103.3 ± 7.92	**< 0.001**
aPWV (m/s)	4.96 ± 0.43	5.02 ± 0.44	4.79 ± 0.32	**< 0.001**

BMI, body mass index; BSA, body surface area; bSBP, brachial systolic blood pressure; bDBP, brachial diastolic blood pressure; MET, metabolic equivalent; cIMT, carotid intima-media thickness; cIDR, carotid intima-media thickness÷carotid diameter ratio; AC, arterial compliance; β, beta stiffness index; Ep, elastic modulus; PWVβ, carotid pulse wave velocity; cSBP, central systolic blood pressure; aPWV, aortic pulse wave velocity. Significant results are marked in bold.

TABLE 2 | SDS values of parameters of body height, BMI, blood pressure, physical performance and vascular properties.

	M ± SD	*p* value
Body height SDS	0.37 ± 1.14	**< 0.001**
BMI SDS	0.02 ± 0.77	0.684
bSBP SDS	0.03 ± 0.95	0.561
bDBP SDS	−0.45 ± 0.91	**< 0.001**
Maximum power output SDS	1.85 ± 1.15	**< 0.001**
cIMT SDS	0.37 ± 1.34	**< 0.001**
Carotid diameter SDS	0.08 ± 0.98	0.133
cIDR SDS	0.20 ± 1.41	**0.009**
AC SDS	0.99 ± 0.83	**< 0.001**
β SDS	−0.75 ± 0.88	**< 0.001**
Ep SDS	−0.88 ± 0.93	**< 0.001**
PWVβ SDS	−1.04 ± 0.97	**< 0.001**
cSBP SDS	0.42 ± 1.29	**< 0.001**
aPWV SDS	0.55 ± 1.33	**< 0.001**

BMI, body mass index; bSBP, brachial systolic blood pressure; bDBP, brachial diastolic blood pressure; cIMT, carotid intima-media thickness; cIDR, carotid intima-media thickness÷carotid diameter ratio; AC, arterial compliance; β, beta stiffness index; Ep, elastic modulus; PWVβ, carotid pulse wave velocity; cSBP, central systolic blood pressure; aPWV, aortic pulse wave velocity. Significant results are marked in bold.

and inter-observer CV of all stiffness parameters (1.46 and 5.57). Intra-observer CV was highest in Ep (4.49) and inter-observer CV was highest in β (13.54).

TABLE 3 | Intra- and inter-observer reliability of ultrasound parameters (coefficient of variation).

	Intra-observer	Inter-observer
cIMT	0.58	2.09
Carotid diameter	0.87	3.63
cIDR	0.81	4.38
AC	1.63	6.59
β	3.40	13.54
Ep	4.49	13.11
PWVβ	1.46	5.57

cIMT, carotid intima-media thickness; cIDR, carotid intima-media thickness÷carotid diameter ratio; AC, arterial compliance; β, beta stiffness index; Ep, elastic modulus; PWVβ, carotid pulse wave velocity.

Parameters of Arterial Structure

Study participants had a mean cIMT of 0.48 ± 0.04 mm, a carotid diameter of 5.65 ± 0.45 mm, and a cIDR of 0.09 ± 0.01% (**Table 1**). Boys had thicker cIMT (0.49 ± 0.04 mm vs. 0.47 ± 0.04 mm, $p < 0.001$) and larger carotid diameters (5.68 ± 0.46 mm vs. 5.56 ± 0.40 mm, $p = 0.034$) than girls. The cIDR was similar between sexes. A total of 135 young athletes (40.8%) had cIMT >75th percentile, 88 (26.6%) had carotid diameter >75th percentile, and 124 (37.5%) exhibited cIDR >75th percentile.

Parameters of Arterial Function

The bSBP was significantly higher in boys than in girls (116.5 ± 9.51 mmHg vs. 113.1 ± 8.00 mmHg, $p = 0.004$, **Table 1**). Systolic and diastolic hypertension were observed in 17 (5.1%) and 3 (0.9%) subjects, respectively. Boys had higher cSBP (107.4 ± 10.4 mmHg vs. 103.3 ± 7.92 mmHg, $p < 0.001$) and aPWV (5.02 ± 0.44 m/s vs. 4.79 ± 0.32 m/s, $p < 0.001$) than girls. AC, Ep, β, and PWVβ were not significantly different. A total of 71 young athletes (21.5%) had cSBP >90th percentile and 94 (28.4%) had aPWV >90th percentile.

Comparison of Structural and Functional Parameters to Normative Values

Young athletes showed thicker cIMT SDS (0.37 ± 1.34, $p < 0.001$) and higher cIDR SDS (0.20 ± 1.41, $p = 0.009$) (**Table 2**, **Figure 2**). Study participants had improved arterial elasticity, as indicated by the AC SDS (0.99 ± 0.83, $p < 0.001$) and reduced peripheral arterial stiffness parameters, including β SDS (−0.75 ± 0.88, $p < 0.001$), Ep SDS (−0.88 ± 0.93, $p < 0.001$), and PWVβ SDS (−1.04 ± 0.97, $p < 0.001$) compared to the reference cohort. In contrast, central stiffness parameters cSBP SDS (0.42 ± 1.29, $p < 0.001$) and aPWV SDS (0.55 ± 1.33, $p < 0.001$) were higher in the young athletes compared to reference values.

In a sub analysis with strength endurance athletes only ($n = 241$), cIMT SDS (0.46 ± 1.36, $p < 0.001$), cIDR SDS (0.35 ± 1.37, $p < 0.001$), AC SDS (1.06 ± 0.83, $p < 0.001$), β SDS (−0.84 ± 0.87, $p < 0.001$), Ep SDS (- 1.00 ± 0.93, $p < 0.001$), PWVβ SDS (−1.16 ± 0.96, $p < 0.001$), cSBP SDS (0.40 ± 1.21, $p < 0.001$), and aPWV SDS (0.55 ± 1.27, $p < 0.001$), but not carotid diameter (−0.01 ± 0.98, $p = 0.990$) were significantly different compared to "0".

DISCUSSION

To the best of our knowledge, this is the first study to investigate the vascular structure and function in young athletes. The cIMT and cIDR were higher in young athletes compared to reference cohorts. Furthermore, young athletes presented better carotid elasticity and lower carotid stiffness (β, Ep, PWVβ) but higher central arterial stiffness (cSBP, aPWV) compared to their peers.

The young athletes were physically active for 565.6 ± 206.0 min/week in sports clubs, which was about 6 h longer than individuals in a representative German sample (Rauner et al., 2015). The maximum power output with an SDS of 1.85 ± 1.15 was higher than the values in the reference population of Blanchard et al. (2018). Therefore, we assume that the young athletes in this study are more physically active and efficient than average.

In our study, we found higher cIMT and cIDR compared to a healthy reference cohort and 40.8% of the young athletes had cIMT >75th percentile. The results of our study contradict Thijssen et al. (2012), who concluded that exercise has no significant effect on vascular properties in the young. Adaptation to exercise is well described in adult athletes; however, only one study investigated cIMT in adolescent athletes. This study demonstrated that cIMT was lower in adolescent wrestlers than in controls (Demirel et al., 2019). However, the large cIMT deviation in the study by Demirel et al. (2019) relative to our study may have impaired the comparability of the two studies; additionally, different ultrasound devices were used in the two studies which also limits comparability. The reference values of Weberruß et al. (2015) are age- and sex-specific. However, cIMT also increases with higher body height (Doyon et al., 2013). Since our study population has a significantly higher body height SDS (see **Table 2**), it cannot be excluded that the higher body size influences the high prevalence of cIMT >75th percentile.

According to Liu et al. (2015), maximum, mean, and minimum arterial diameters in young adult basketball players were improved compared to sedentary controls. We did not observe significant changes in arterial diameter in our population of young athletes compared to the reference cohort. Remodeling of the arterial diameter may be dependent on the physically active limb (Green et al., 2017). Huonker et al. (2003) showed that the diastolic diameter of the subclavian artery was higher in tennis players and that the diastolic diameter of the femoral artery was higher in cyclists than in untrained controls. Furthermore, in below-knee amputated athletes, the diastolic diameter of the femoral artery in the intact limb was higher than on the lesion side (Huonker et al., 2003). Approximately two-thirds of the young athletes in our study exercised in sports involving lower limb movement. To investigate local remodeling due to exercise in young people, the examined artery should be selected based on the type of exercise performed.

Carotid function improved in our athletic population compared to a healthy reference cohort, indicated by higher carotid elasticity (AC) and reduced carotid stiffness (β, Ep, and PWVβ). Our results are in agreement with Nishiwaki et al. (2017), who reported lower cardio-ankle vascular index in young adult cyclists and reduced brachial-ankle PWV in both cyclists and swimmers than in controls. Furthermore, ultrasound-derived β and Ep of the CCA were lower in ten young adult basketball players than in sedentary controls (Liu et al., 2015). In addition, higher flow-mediated dilation was observed in young adult athletes than in inactive controls (Podgorska et al., 2017).

However, central hemodynamic parameters, including aPWV and cSBP, were higher in our cohort compared to the appropriate reference values, indicating higher aortic stiffness in young athletes. The same vascular effects were observed in middle-aged marathon runners. Participants in this study had significantly higher bSBP, bDBP, aortic SBP, aortic DBP, and PWV compared to controls (Vlachopoulos et al., 2010). Coates et al. (2018) compared vascular changes after 3 weeks of regular exercise training (regular training load) and 3 weeks of overload training (150% of regular training load) in 26 endurance athletes between 18 and 50 years; carotid-femoral PWV significantly increased in the overload group, indicating that overload training induced central arterial stiffening. Because aPWV and BP are not only age- and sex- but also height-dependent, it cannot be excluded that the higher body height in our study population influences the higher SDS values of aPWV and cSBP (Reusz et al., 2010; Regnault et al., 2014).

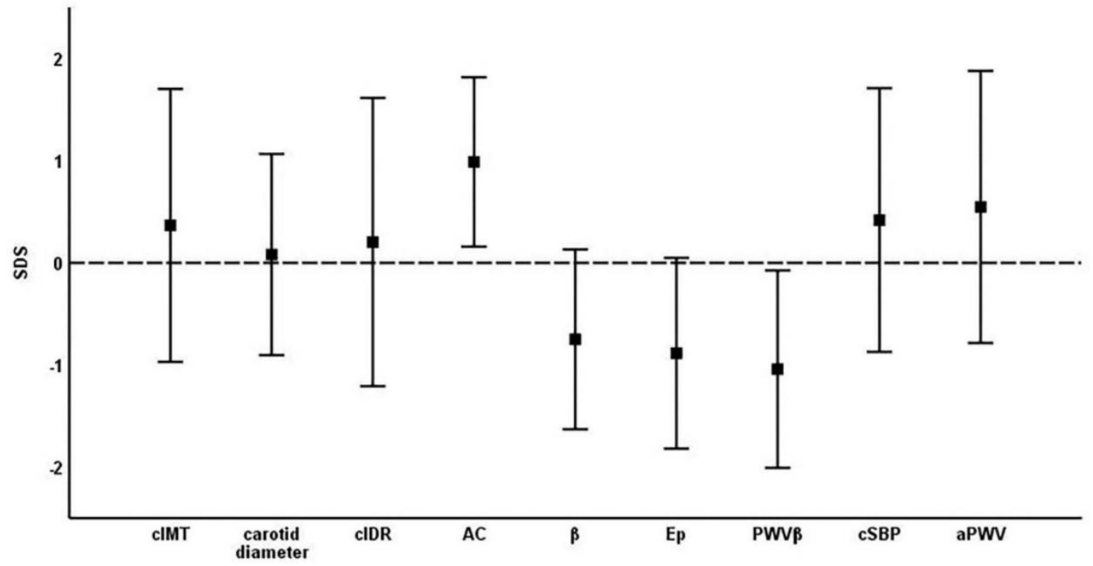

FIGURE 2 | Mean ± standard deviation of SDS of vascular parameters. cIMT, carotid intima-media thickness; cIDR, carotid intima-media thickness÷carotid diameter ratio; AC, arterial compliance; β, beta stiffness index; Ep, elastic modulus; PWVβ, carotid pulse wave velocity; cSBP, central systolic blood pressure; aPWV, aortic pulse wave velocity.

Sport types, especially endurance and strength training, have different impacts on vascular function. While endurance exercise is associated with a decrease in arterial stiffness, athletes participating in strength exercise exhibit elevated arterial stiffness (Bertovic et al., 1999; Otsuki et al., 2007; D'Andrea et al., 2012). During the competitive season, bSBP and bDBP increased in American-style football players and central aortic pulse pressure and PWV were significantly higher after season, measured by applanation tonometry (Kim et al., 2015). Furthermore, powerlifting athletes showed reduced cSBP after a 12-week strength program (Jürgenson et al., 2019). In contrast to our findings, Demirel et al. (2019) compared ultrasound measurements of the CCA in adolescent wrestlers and sedentary controls and found no significant differences in distensibility, elastic modulus, and compliance of the CCA. The differences in the study population (young athletes of various types of sport vs. adolescent wrestlers) between our study and Demirel et al. (2019) could explain the discrepancies in these results.

In addition to the distinction between endurance and strength sports, training experience may also influence arterial stiffness. Otsuki et al. (2007) examined endurance-trained men with a short and a long career in competitive sports vs. strength-trained men with a short and long career in competitive sports and compared results to sedentary controls. Endurance athletes with a long competitive career, but not those with a short competitive career, had lower aPWV than sedentary controls. Furthermore, aPWV was higher in strength athletes with both short and long competitive careers than in sedentary controls. The authors concluded that longer experience in endurance training positively influenced aPWV, but the higher the number of strength exercises within a sporting activity, the higher (worse) the aPWV.

The classification of different types of sports into "endurance sports" or "strength sports" categories is difficult. For example, ball sports, like soccer or basketball, predominantly consist of an endurance component but also involve strength components. Athletic training has gained importance, even at a young age, as a means of improving cardiopulmonary and muscular endurance and high-speed strength. The young athletes in our study mainly participated in cardiopulmonary endurance sports and had trained for 3.65 ± 2.51 years. This might explain the higher aPWV and cSBP in our study population. A comparison of young athletes participating in endurance, muscular endurance, or strength sports could provide detailed information on possible differences in arterial stiffness between sport types.

40.8% of young athletes showed cIMT >75th percentile. The high cIMT could indicate preliminary stages of atherosclerosis in young athletes and, thus, a negative effect of competitive sports on these vessels. The development of atherosclerosis begins in childhood and adolescence, when low-density lipoprotein particles enter and accumulate in the intimal layer. During the inflammatory process, endothelial cells are activated and secrete adhesion molecules, leading to the formation of foam cells via a complex process (Insull, 2009). Besides morphometric alterations of the arterial wall, including intimal thickening, the atherosclerotic process also leads to a decreased endothelial function and, therefore, increase in arterial stiffness. Therefore, arterial wall thickening and reduced elasticity indicate that competitive sports in adolescence may have a pathological effect on vascular health. However, young athletes exhibited improved elasticity and wall thickening and higher cIDR. Arterial segments with higher wall-to-lumen ratios have better arterial function (Thijssen et al., 2011). The underlying mechanism seems to be the greater number of VSMC in the arterial wall and an enhanced response to vasodilating stimuli (Thijssen et al., 2011; Green et al., 2017). Thus, the thickening of the intima-media complex in combination with improved carotid function indicates VSMC proliferation in the tunica media, improved vascular reactivity and, therefore, a functional adaptation to exercise.

Limitations

This study has several limitations. First, aortic stiffness was only estimated via the ARCSolver Algorithm and not directly measured. A recent report on the technical effectiveness of the ARCSolver Algorithm showed that cSBP measurement is reliable, but aPWV is slightly overestimated (EUnetHTA OTCA-24 Assessment Team, 2020). Second, the methodology of measuring bSBP and bDBP in our study (Mobil-O-Graph) differs from the measurement in the reference population (Datascope Accutorr Plus). Sarganas et al. (2020) compared the BP values of both devices and found that the Mobil-O-Graph provided higher values than the Datascope Accutorr Plus. Although the validation was only carried out in adults aged 21 and older, it is possible that this tendency is already evident in children and adolescents. Third, pubertal status was not assessed and, therefore, not included in the analysis as a factor influencing the results. Although it is known that pubertal status influences vascular properties (Drole Torkar et al., 2020), it was not possible to include the assessment via Tanner Scale into this setting due to child protection concerns (McClean et al., 2018). Fourth, the types of sports are unequally distributed within our study population. This limitation is related to patient recruitment. Even though the associations of different types of sports support and suggest pre-participation screening, mainly male soccer players were included in the study. Young athletes from other types of sports and girls are underrepresented. Fifth, CCA, as a parameter of arterial structure and function, is used for generalized systemic adaptations to exercise. Different types of sports can have a different impact on CCA, but they could have also stimulated local arteries (e.g., brachial or femoral). Sixth, we did not consider the proportion of exercise training spent in endurance vs. strength sports and the timing of the examination (preseason, during season, and postseason), although both aspects are known to influence cardiac adaptation or the adaptation of physical performance to exercise (Dores et al., 2015; Emmonds et al., 2020). Therefore, we can conclude in general that young athletes differ in their vascular properties from controls, but we are not able to conclude that strength and/or endurance athletes differ from the reference collective. In order to investigate the long-term effects of different types of sports and training levels on vascular parameters in young athletes, we are currently conducting a long-term study (Baumgartner et al., 2019).

With regard to intra-observer variability, the scatter between the two measurements (CV $< 5\%$ in all parameters) was very low; the intra-observer CV of the structural parameters was slightly lower than that of the functional parameters. Compared to previous studies, the intra-observer variability of structural and functional parameters was lower (Kanters et al., 1998; Iannuzzi et al., 2008; Böhm et al., 2009; Bjällmark et al., 2010). The inter-observer variability of the structural parameters was also lower in our study compared to the literature (Böhm et al., 2009). The CV of the inter-observer variability of stiffness parameters β and Ep was higher compared to Weberruß et al. (2015) but lower than Kanters et al. (1998). In summary, both intra- and inter-observer variabilities of the ultrasound parameters were acceptable to confirm the good quality of the data.

CONCLUSION

In summary, we observed improved carotid elasticity but altered central hemodynamics and carotid structure in young athletes compared to a reference cohort. The investigation of vascular properties in young athletes is new and rarely performed. The paucity of studies in young athletes is due to the perceived lack of medical need for these measurements in young athletes, in contrast to ECG or echocardiography. However, our results indicate that competitive sports in youth can alter vascular properties.

DATA AVAILABILITY STATEMENT

The datasets analyzed within the study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Technical University of Munich (project numbers 301/18 S and 131/19 S-SR). Written informed consent to participate in this study was provided by the participants' legal guardian.

AUTHOR CONTRIBUTIONS

LB, HW, TS, and RO-F designed the study. LB, KA, TE, and DG performed the data collection. LB performed the data analysis and drafted the manuscript. All authors reviewed, edited, and approved the manuscript.

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3.4 Article 4

Authors: Lisa Baumgartner, Heidi Weberruß, Tobias Engl, Renate Oberhoffer-Fritz, Thorsten Schulz

Title: Exercise Training Duration and Intensity Are Associated With Thicker Carotid Intima-Media Thickness but Improved Arterial Elasticity in Active Children and Adolescents

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Summary:

Physical activity is one of the most crucial prevention strategies to avoid cardiovascular disease. In children and adolescents, better vascular properties such as thinner cIMT and improved arterial elasticity were observed concerning physical activity. However, this association has been described for overall physical activity rather than explicitly for those children and adolescents who exercise in sports clubs. Therefore, this study aimed to investigate the relationship between exercise training duration and intensity with vascular properties of children and adolescents who are active in sports clubs. For this study, only those aged 8 to 17 years who were engaged in sports clubs, had no cardiovascular or metabolic disease and had a vascular measurement were included in the total sample. Furthermore, if the children and adolescents visited our sports medicine outpatient clinic more than once during this period, only the first examination was considered. The same vascular analyses as described in Article 3 were performed. Training duration and intensity were assessed using the MoMo-AFB. In addition to linear relationships between vascular properties and exercise duration and intensity, quintile analyses were performed to determine whether children and adolescents with an extremely high exercise load showed differences in vascular properties compared with children and adolescents with a lower exercise load. Higher quintiles corresponded to a higher training duration or intensity. The main finding of this study is that higher training duration and intensity were associated with higher cIMT. These associations were also observed when boys were considered alone, whereas girls only demonstrated better functionality of the CCA. While lower central stiffness was apparent in the overall analysis of all children and adolescents and separately in boys, a larger carotid diameter was observed with higher training intensity in the overall analysis. Analogous to the results of the regression analyses, children and adolescents in quintiles Q4 and Q5 of training duration showed thicker cIMT compared with quintiles Q1 and Q2. Children and

adolescents in quintile Q5 of training duration had simultaneously lower cSBP than quintiles Q1 and Q2. In the quintile analyses of training intensity, subjects in quintile Q5 also had the highest cIMT. The higher cIMT combined with improved elasticity of the CCA suggests a functional adaptation of the CCA to increased training loads. This is indicated by the lower central vascular stiffness associated with a higher training load. Nevertheless, especially those children and adolescents with very high training loads should continue to be examined to prevent a manifestation of thickened cIMT which leads to negative consequences for the health of these children and adolescents.

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Individual contribution:

Lisa Baumgartner was the principal investigator of this article. Lisa Baumgartner, Heidi Weberruß, Thorsten Schulz, and Renate Oberhoffer-Fritz designed the study and engaged in acquiring the funding. Lisa Baumgartner (ultrasound, Mobil-O-Graph®, MoMo-AFB) and Tobias Engl (Mobil-O-Graph®) collected the data. Lisa Baumgartner performed the data analysis and wrote the manuscript. All authors revised the manuscript and approved the final version.

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ORIGINAL RESEARCH
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Exercise Training Duration and Intensity Are Associated With Thicker Carotid Intima-Media Thickness but Improved Arterial Elasticity in Active Children and Adolescents

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Even though exercise generally has a positive effect on health, intensive exercise can have adverse effects on the vascular system of adults. This study aimed to investigate the association between training duration and intensity and vascular structure and function in 427 physically active children and adolescents (14.0 ± 1.94 years). In this study, we examined carotid intima-media thickness (cIMT), carotid diameter, and cIMT:diameter-ratio as parameters of carotid arterial structure and arterial compliance (AC), stiffness index β (β), elastic modulus (Ep), and carotid pulse wave velocity (PWVβ) as parameters of carotid arterial function with high-resolution ultrasound. We collected central systolic blood pressure (cSBP) and aortic pulse wave velocity (aPWV) as parameters of central arterial stiffness with an oscillometric device. We used the MoMo Physical Activity Questionnaire to record training duration and intensity. Training duration ($p = 0.022$) and intensity ($p = 0.024$) were associated with higher cIMT. Further, training duration was associated with lower central arterial stiffness (cSBP: $p = 0.001$; aPWV: $p = 0.033$) and improved AC ($p < 0.001$). Higher training intensity was related to improved AC ($p < 0.001$) and larger carotid diameter ($p = 0.040$). Boys presented thicker cIMT ($p = 0.010$), improved AC ($p = 0.006$), and lower central arterial stiffness (cSBP: $p < 0.001$; aPWV: $p = 0.016$) associated with higher training duration. Girls presented improved AC ($p = 0.023$) and lower Ep ($p = 0.038$) but higher β ($p = 0.036$) associated with higher training duration. Only boys demonstrated thicker cIMT ($p = 0.016$) and improved AC ($p = 0.002$) associated with higher training intensity. A quintile analyses of the training duration revealed thicker cIMT of children and adolescents in Q1 and Q5 than that in Q4 and Q5. Besides, Q1 showed lower cSBP compared to Q4 and Q5. Regarding training intensity, Q5 had thicker cIMT than Q2 and Q3. Although a higher training load is associated with thicker cIMT, the common carotid artery is also more elastic. This suggests that a higher training load leads to a functional adaptation of the carotid artery in youth.

Keywords: arterial elasticity, arterial stiffness, exercise load, carotid intima - media thickness, youth

INTRODUCTION

In adults, greater exposure to cardiovascular risk factors such as obesity is related to thicker arterial walls, and exercise training is associated with a thinner arterial wall (1). Similarly, exercise training is associated with improved vascular function and the presence of cardiovascular risk factors with reduced vascular function (2). The term "athlete's artery" summarizes the vascular adaptations to exercise, analogous to cardiac adaptations to exercise and the term "athlete's heart." The "athlete's artery" is characterized by lower wall thickness, higher lumen or diameter, and lower arterial stiffness (3). Arterial structure and function measurements are divided into central (aorta) and peripheral (e.g., carotid or brachial artery) measurements.

Even though exercise generally has a positive effect on health, high volume exercise can have adverse effects on the vascular system. Müller et al. (4) found a significant increase in carotid intima-media thickness (cIMT) in male marathon runners within 4 years, which was contrary to the postulated reduced wall thickness. Another study showed that higher central systolic blood pressure (cSBP) and aortic pulse wave velocity (aPWV) were observed in predominantly male marathon runners (5). Also, strength-trained men showed higher arterial stiffness that may depict early subclinical vascular dysfunction (6–8).

Also, training frequency and training volume have a significant effect on the extent of cardiovascular adaptation (6, 9, 10). Aengevaeren et al. (10) investigated the extent of coronary artery calcification (CAC), plaque characteristics, and exercise volumes [metabolic equivalent of task (MET)] in men who participated in competitive and recreational sports. They observed an odds ratio (OR) of 3.3 in the prevalence of atherosclerotic plaques, with a training volume of >2,000 MET-min/week, and an OR of 3.2 with a CAC score of > 0 compared with persons with a volume of <1,000 MET-min/week. Recently, studies have also been performed in pediatric populations for the first time. A study observed better carotid elasticity but higher cIMT and cIMT÷carotid diameter-ratio (cIDR) and higher central arterial stiffness in young athletes (11). Another study found lower cIMT in male adolescent wrestlers than in controls, but there were no differences in cIMT and vascular function observed in young male athletes participating in dynamic or strength sports (12, 13).

There is no evidence of the impact of training behavior on vascular health in the overall population of healthy active children and adolescents although overall physical activity is considered to have a positive effect on vascular properties in childhood and adolescence (14). Besides, the studies conducted so far have mainly involved male subjects. Therefore, to what extent vascular properties differ between young active girls and boys and whether exercise in sports clubs has a different effect on vascular properties between sexes is not clear. Furthermore, the relationship between different training frequencies and intensities on the vascular system in youth has not been studied sufficiently.

Thus, this study aimed to investigate the association between training duration and intensity and the vascular structure and function in physically active children and adolescents, overall and separated for boys and girls. We hypothesized that there is an association between higher training duration and intensity and better vascular properties in both sexes. We also examined the differences in vascular properties between quintiles of training duration and intensity to study whether vascular properties follow a curved pattern associated with higher training load.

METHODS

Study Design and Study Participants

In our pediatric department, a total of 734 children and adolescents, regularly exercising in sports club activities, were enrolled in a pre-participation screening. The recruitment started in November 2017 and lasted until September 2020. Of these 734 subjects, 108 were examined twice, 32 three times and 3 four times, as these subjects received annual pre-participation screening. In this case, only the first examination was considered and the 181 multiple measurement were not included. In 88 subjects, the vascular measurements could not be performed and we excluded 38 subjects because of their age (<8.00 or >17.25 years). Thus, the analyzed dataset was comprised of 427 healthy participants (25.0% females) aged between 8 and 17 years.

The data collection was part of the Munich Cardiovascular Adaptation in Young Athletes study (MuCAYA study, data from September 2018 to September 2020) and the upstream pilot study (data from November 2017 to September 2018) (15). Both studies were approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki (projects numbers 301/18 S and 131/19 S-SR). All children and/or their legal guardians provided written informed consent before the examinations.

Assessment of Body Size and Body Surface Area

We measured the body height and body mass of the participants without shoes, wearing light sports clothing in an upright position, with straight shoulders, and looking ahead. The body mass was determined precisely at 0.1 kg and body size at 0.1 cm (seca 799, seca GmbH & Co. KG, Hamburg, Germany). The body mass index (BMI) was calculated by dividing body mass (kg) by body height squared (m^2). Based on the German reference data, standard deviation score (SDS) of BMI was calculated (16). According to Dubois and Dubois (17), the body surface area (BSA) was calculated.

Assessment of Blood Pressure and Central Arterial Stiffness

Using the oscillometric device Mobil-O-Graph (IEM, Stolberg, Germany), brachial systolic blood pressure (bSBP), diastolic blood pressure (bDBP), cSBP, and aPWV were measured automatically on the left arm in a supine position after 10 min of rest. Depending on the circumference of the upper arm, the cuff size was selected. cSBP of the Mobil-O-Graph device has been validated in comparison to the SphycmoCor device and radial tonometry (18, 19) and aPWV in comparison to intracatheter measurements (20). cSBP and aPWV were computed using the ARCSolver algorithm (Austrian Institute of Technology, Vienna, Austria).

Assessment of Carotid Structure and Function

We used semi-automated ultrasound with a high frequency linear array probe of 5–13 MHz (Aloka Prosound α7, Hitachi Medical Systems GmbH, Wiesbaden, Germany) to measure carotid structure and function in a supine position after 10 min of rest. Carotid arterial properties, were taken from the left and right common carotid artery (CCA), 1 cm proximal to the carotid bulb using B- and M-Mode ultrasound. On each side, cIMT was measured during diastole at two angles (right, 120° and 150°; left, 240° and 210°) at the end of diastole on the CCA far wall (15). Furthermore, carotid diameter and function were examined using the eTracking method twice on each side (right, 150°; left, 210°). The carotid diameter was measured in systole (D_{max}) and diastole (D_{min}) but only D_{min} was used for further analysis and calculation of cIDR, corresponding to cIMT measured at diastole, and is denoted as carotid diameter in this document. Parameters of carotid function, including arterial compliance (AC), elastic modulus (Ep), stiffness index β (β), and local PWV at the CCA (PWVβ), were calculated using the following formula (15, 21–24):

$$AC = \pi \frac{(D_{max^2} - D_{min^2})}{4\,(bSBP_{max} - bDBP_{min})} \quad (1)$$

$$Ep = \frac{bSBP_{max} - bDBP_{min}}{\frac{D_{max} - D_{min}}{D_{min}}} \quad (2)$$

$$\beta = \frac{\ln \frac{bSBP_{max}}{bDBP_{min}}}{\frac{D_{max} - D_{min}}{D_{min}}} \quad (3)$$

$$PWV\beta = \sqrt{\frac{\beta * bDBP_{min}}{2\rho}} \quad (4)$$

All parameters were calculated as average values of four measurements. All measurements were conducted by two investigators. The analysis of the inter-observer variability revealed a small to acceptable deviation (11).

Assessment of Training Duration and Intensity

All children and adolescents completed the MoMo Physical Activity Questionnaire (MoMo-PAQ) for pupils (25, 26). The questionnaire records self-reported physical activity in different settings (school, everyday activities, sports clubs, leisure-time outside of sports clubs) regarding the amount (min/day) and intensity (low, moderate, intense), which allows the calculation of sports-specific MET values (27). Physical activity at school, everyday activities, and leisure time physical activity outside of sports clubs were not considered, because this study focuses only on the training behavior in sports clubs but not on the overall activity in all settings.

The estimated intraclass correlation for reliability of sports club activities was 0.64 ($p < 0.01$) in overall, 0.49 ($p < 0.01$) for boys, 0.78 ($p < 0.01$) for girls, 0.45 ($p < 0.01$) for children, and 0.90 ($p < 0.01$) for adolescents (28). Validity was assessed in comparison with the Actigraph GT1M activity monitor ($r = 0.35$, $p < 0.01$) and the Previous Day Physical Activity Recall self-report instrument ($r = 0.55$, $p < 0.01$) (28).

Our subjects reported the weekly amount of physical activity spent in the type of sport (without outward and return, changing clothes, and showering) and the number of months in which the weekly amount of physical activity was performed. We calculated the weekly minutes spent in sports clubs and thus training duration using the following formula:

$$training\ duration = minutes\ per\ week * \frac{number\ of\ months}{12} \quad (5)$$

Depending on the reported intensity level, an individual MET score was assigned to every recorded type of sport (27, 29, 30). MET-min/week spent in sports clubs was calculated and then divided by 60 to obtain the MET-hours-index:

$$training\ intensity = \frac{training\ duration * MET}{60} \quad (6)$$

To assess training history, the participants were asked how many years they had been performing their major type of sport.

Statistical Analysis

We used SPSS version 25.0 (SPSS Inc., Chicago, IL, USA) for all statistical analyses. The level of significance was set at $p < 0.05$. Continuous variables are presented as mean ± standard deviation and categorical variables as n (%). Sex differences were analyzed using an independent t-test. The association between training duration and intensity and vascular parameters was assessed using multiple linear regression analyses. All regression models were adjusted for age, sex, BSA, and training years (31–33). Regression models with parameters of carotid arterial structure were adjusted further for bSBP (31). All regression models were repeated separately for boys and girls. The differences in parameters of vascular structure and function between quintiles of training duration and intensity were examined using analysis of covariance (ANCOVA) with Bonferroni *post hoc* tests. Based on the distribution of training duration and intensity within the dataset, the classification in quintiles was conducted. Regarding the quintiles of training duration, Q1 referred to a training duration of up to 330.0 min/week, Q2 from 330.1 to 412.5 min/week, Q3 from 412.6 to 481.5 min/week, Q4 from 481.6 to 626.0 min/week, and Q5 above 626.0 min/week. Regarding the quintiles of training intensity, Q1 referred to a training intensity of up to 49.5 MET-hours-index, Q2 from 49.6 to 64.2 MET-hours-index, Q3 from 64.3 to 80.0 MET-hours-index, Q4 from 80.1 to 99.0 MET-hours-index, and Q5 above 99.0 MET-hours-index. The ANCOVAs were adjusted for the same variables as in the regression models.

RESULTS

The study collective had a mean age of 14.0 ± 1.94 years and spent 491.9 ± 224.7 min/week in sports club activities (**Table 1**). Children and adolescents participated in 36 different

TABLE 1 | Study characteristics.

	Total		Boys		Girls		p
	n	M ± SD	n	M ± SD	n	M ± SD	
Age (y)	427	14.0 ± 1.94	320	14.0 ± 1.94	107	13.9 ± 1.96	0.458
Body mass (kg)	427	55.4 ± 14.6	320	56.2 ± 15.4	107	53.0 ± 11.9	**0.024**
Body height (cm)	427	166.2 ± 14.5	320	167.6 ± 15.1	107	161.9 ± 11.8	**<0.001**
BMI (kg/m²)	427	19.7 ± 2.72	320	19.6 ± 2.72	107	19.9 ± 2.74	0.272
BMI SDS	427	0.020 ± 0.796	320	0.001 ± 0.802	107	0.078 ± 0.777	0.384
BSA (m²)	427	1.59 ± 0.28	320	1.61 ± 0.29	107	1.54 ± 0.23	**0.008**
bSBP (mm Hg)	427	115.0 ± 10.2	320	115.8 ± 10.9	107	112.7 ± 7.74	**0.002**
bDBP (mm Hg)	427	65.2 ± 6.26	320	65.2 ± 6.35	107	65.2 ± 6.00	0.978
Training duration (min/week)	427	491.9 ± 224.7	320	489.9 ± 212.3	107	495.7 ± 259.3	0.856
Training intensity (MET-hours-index)	424	76.4 ± 36.1	318	76.9 ± 31.8	106	74.7 ± 46.9	0.640
Training years (y)	395	3.43 ± 2.53	296	3.54 ± 2.64	99	3.13 ± 2.24	0.152
cIMT (mm)	427	0.47 ± 0.04	320	0.48 ± 0.04	107	0.46 ± 0.04	**<0.001**
Carotid diameter (mm)	422	5.63 ± 0.46	316	5.66 ± 0.47	106	5.52 ± 0.42	**0.006**
cIDR	422	0.085 ± 0.009	316	0.085 ± 0.009	106	0.083 ± 0.009	**0.039**
AC (mm²/kPa)	422	1.52 ± 0.33	316	1.55 ± 0.33	106	1.45 ± 0.31	**0.008**
β	422	3.20 ± 0.74	316	3.18 ± 0.73	106	3.28 ± 0.81	0.273
Ep (kPa)	422	37.5 ± 9.11	316	37.4 ± 8.86	106	38.2 ± 10.0	0.423
PWVβ (m/s)	422	3.61 ± 0.39	316	3.60 ± 0.38	106	3.65 ± 0.44	0.259
cSBP (mm Hg)	427	105.1 ± 10.8	320	105.9 ± 11.4	107	102.5 ± 8.40	**0.001**
aPWV (m/s)	427	4.89 ± 0.45	320	4.93 ± 0.48	107	4.74 ± 0.32	**<0.001**

BMI, Body mass index; SDS, standard deviation score; BSA, body surface area; bSBP, brachial systolic blood pressure; bDBP, brachial diastolic blood pressure; MET, metabolic equivalent; cIMT, carotid intima-media thickness; cIDR, carotid intima-media thickness:carotid diameter-ratio; AC, arterial compliance; β, beta stiffness index; Ep, elastic modulus; PWVβ, carotid pulse wave velocity; cSBP, central systolic blood pressure; aPWV, aortic pulse wave velocity. Significant results are marked in bold.

types of sports. Soccer (36.8%), volleyball (9.4%), hockey (8.7%), wrestling (6.8%), and cross-country skiing (5.6%) were the main types of sports. Active boys had significantly higher body height, body mass, BSA, bSBP, cIMT, carotid diameter, cIDR, AC, cSBP, and aPWV than girls (**Table 1**). BMI SDS was 0.001 ± 0.802 in boys and 0.078 ± 0.777 in girls. Of 427 subjects, 26 (6.1%) had isolated bSBP >95th percentile, one (0.2%) had isolated bDBP >95th percentile, and five (1.2%) subjects presented combined bSBP and bDBP >95th percentile (34).

Multiple linear regressions with training duration revealed a significant positive association with cIMT (std. $\beta = 0.113$, $p = 0.022$), but not with carotid diameter or cIDR (**Table 2**). Higher training duration was also related to higher AC (std. $\beta = 0.184$, $p = < 0.001$), but not to parameters of carotid arterial stiffness. A higher number of minutes spent in sports club activities was associated with lower cSBP (std. $\beta = -0.139$, $p = 0.001$) and aPWV (std. $\beta = -0.085$, $p = 0.033$).

Multiple linear regressions with training intensity revealed a significant positive association with cIMT (std. $\beta = 0.111$, $p = 0.024$) and carotid diameter (std. $\beta = 0.105$, $p = 0.040$), but not with cIDR (**Table 3**). Higher training intensity was also related to higher AC (std. $\beta = 0.179$, $p < 0.001$), but not to carotid arterial stiffness. Neither of central arterial stiffness parameters (cSBP and aPWV) was associated with training intensity.

Multiple linear regression models were performed separated for boys and girls for identifying sex-specific differences in the association between vascular parameters and training duration

TABLE 2 | Association between training duration (min/week) and vascular properties in active children and adolescents.

	n	β	Std. β	p	R^2
cIMT* (mm)	395	0.00002	0.113	**0.022**	0.183
Carotid diameter* (mm)	392	0.0002	0.081	0.111	0.122
cIDR*	392	0.000001	0.030	0.573	0.021
AC⁺ (mm²/kPa)	392	0.0003	0.184	**<0.001**	0.116
β⁺	392	−0.0002	−0.046	0.366	0.084
Ep⁺ (kPa)	392	−0.004	−0.094	0.061	0.121
PWVβ⁺ (m/s)	392	−0.0002	−0.092	0.068	0.112
cSBP⁺ (mm Hg)	395	−0.007	−0.139	**0.001**	0.387
aPWV⁺ (m/s)	395	−0.0002	−0.085	**0.033**	0.434

cIMT, carotid intima-media thickness; cIDR, carotid intima-media thickness:carotid diameter-ratio; AC, arterial compliance; β, beta stiffness index; Ep, elastic modulus; PWVβ, carotid pulse wave velocity; cSBP, central systolic blood pressure; aPWV, aortic pulse wave velocity. Significant results are marked in bold.

**Adjusted for age, sex, body surface area, training years, and bSBP.*

+Adjusted for age, sex, body surface area, and training years.

TABLE 3 | Association between training intensity (MET-hours-index) and vascular properties in active children and adolescents.

	n	*β*	Std. *β*	*p*	R^2
cIMT* (mm)	393	0.0001	0.111	**0.024**	0.183
Carotid diameter* (mm)	390	0.001	0.105	**0.040**	0.127
cIDR*	390	0.000003	0.013	0.805	0.019
AC+ (mm^2/kPa)	390	0.002	0.179	**<0.001**	0.115
β+	390	−0.001	−0.033	0.528	0.083
Ep+ (kPa)	390	−0.016	−0.062	0.224	0.116
PWVβ+ (m/s)	390	−0.001	−0.053	0.298	0.107
cSBP+ (mm Hg)	393	−0.018	−0.060	0.162	0.372
aPWV+ (m/s)	393	−0.0004	−0.028	0.493	0.427

cIMT, carotid intima-media thickness; cIDR, carotid intima-media thickness:carotid diameter-ratio; AC, arterial compliance; β, beta stiffness index; Ep, elastic modulus; PWVβ, carotid pulse wave velocity; cSBP, central systolic blood pressure; aPWV, aortic pulse wave velocity. Significant results are marked in bold.

**Adjusted for age, sex, body surface area, training years, and bSBP.*

+Adjusted for age, sex, body surface area, and training years.

and intensity (**Table 4**). A positive association between training duration and cIMT was found in boys (std. $\beta = 0.151$, $p = 0.010$), but not in girls. Neither boys nor girls showed a correlation between carotid diameter and cIDR and training duration, but boys (std. $\beta = 0.161$, $p = 0.006$) and girls (std. $\beta = 0.250$, $p = 0.023$) revealed a positive correlation between AC and training duration. Regarding the parameters of carotid arterial stiffness, a negative correlation between β (std. $\beta = -0.226$, $p = 0.036$) and Ep (std. $\beta = -0.222$, $p = 0.038$) and training duration was found only in girls. On the other hand, a negative association between cSBP (std. $\beta = -0.179$, $p < 0.001$) and aPWV (std. $\beta = -0.130$, $p = 0.005$) and training duration was found only in boys. Concerning training intensity, positive correlations with cIMT (std. $\beta = 0.139$, $p = 0.016$) and AC (std. $\beta = 0.177$, $p = 0.002$) were also found only in boys.

The differences in parameters of carotid arterial structure (adjusted for age, sex, BSA, and bSBP) and arterial function (adjusted for age, sex, and BSA) between quintiles of training duration are shown in **Figure 1**. Q5 and Q4 displayed thicker cIMT than Q1 (Q5 vs. Q1: $p = 0.035$, Q4 vs. Q1: $p = 0.034$) and Q2 (Q5 vs. Q2: $p = 0.012$, Q4 vs. Q2: $p = 0.012$). Furthermore, Q5 showed lower cSBP compared to Q1 ($p = 0.008$) and Q2 ($p = 0.007$). The ANCOVA model showed a tendency of significance for β, Ep and aPWV. There were no differences between the quintiles regarding carotid diameter, cIDR, AC, and PWVβ. Separate quintile plots for girls and boys are provided in the **Supplementary Material**.

The differences in parameters of carotid arterial structure (adjusted for age, sex, BSA, and bSBP) and arterial function (adjusted for age, sex, and BSA) and quintiles of training intensity are shown in **Figure 2**. Q5 displayed thicker cIMT than Q2 ($p = 0.001$) and Q3 ($p = 0.029$). There were no differences between the quintiles in carotid diameter, cIDR, AC, β, Ep, PWVβ, cSBP, and aPWV. Separate quintile plots for girls and boys are provided in the **Supplementary Material**.

DISCUSSION

We found divergent results regarding the association between training duration and intensity and vascular properties in active children and adolescents. Overall, higher training duration and intensity correlated with higher IMT and elasticity of the carotid artery. Higher training duration was related to better central hemodynamics and higher training intensity to larger carotid diameter. Sex-specific analyses revealed better carotid arterial elasticity with higher training duration in boys and girls. Only boys showed better carotid arterial elasticity with higher training intensity and higher training duration with better central hemodynamics. Additionally, higher training duration and intensity was associated with thicker cIMT in boys. Girls, however, showed lower carotid arterial stiffness with higher training duration.

Besides the linear associations, the quintile analyses indicated that active children and adolescents with very high training duration and intensity have a significantly thicker cIMT than children and adolescents with lower training duration and intensity. Furthermore, active children and adolescents with very high training duration showed significantly lower cSBP.

Carotid Artery Structure

cIMT measurement in children and adolescents is mainly used for cardiovascular risk stratification (35). Compared with findings by Weberruß et al. (22) (0.46 ± 0.03 mm in boys and girls), mean cIMT of girls (0.46 ± 0.04 mm) is at a similar level, but mean cIMT of boys (0.48 ± 0.04 mm) is slightly higher in our cohort.

To our knowledge, only Demirel et al. (12) investigated cIMT in an active pediatric population and found lower cIMT in adolescent male wrestlers than age- and sex-matched controls. The comparison of cIMT values indicated a substantial deviation from cIMT observed in this study to cIMT values of Demirel et al. (12) (0.28 mm in athletes, 0.35 mm in controls). This distinction is probably caused by the different measurement methodology, which is a major determinant in cIMT assessment: cIMT measured directly after the bulb is larger than 2–3 cm proximal the bifurcation (36). Demirel et al. (12) measured only on the right carotid artery and 2 cm proximal to the bifurcation, which might explain the deviation in cIMT. cIMT sonography guidelines were published in 2015 to enable the comparison of different studies. These guidelines recommend measuring the cIMT 1 cm proximal to the carotid bulb (35).

Further studies in adult athletes observed lower (37), higher (38), or similar cIMT (39) compared with controls. In general, physical activity has a beneficial effect on the cardiovascular system of individuals. However, the positive effect seems to be reversed with an excessively high activity volume, as several studies have reported adverse effects (4, 10). The U-shaped or reverse J-shaped curve describes that individuals benefit from exercise, even if the exercise exceeds the level recommended for health maintenance and health promotion, until a turning point is reached and positive effects of exercise are reversed at very high exercise loads. In other words, the health benefits of exercise in

TABLE 4 | Sex-specific associations between training duration (min/week) and training intensity (MET-hours-index) and vascular properties in active children and adolescents.

		Boys					Girls				
		n	*β*	Std. *β*	*p*	R^2	*n*	*β*	Std. *β*	*p*	R^2
Training duration (min/week)	cIMT* (mm)	296	0.00003	0.151	**0.010**	0.151	99	0.000002	0.014	0.899	0.064
	Carotid diameter* (mm)	294	0.0003	0.109	0.070	0.105	98	−0.00005	−0.028	0.793	0.179
	cIDR*	294	0.000002	0.045	0.475	0.019	98	0.0000007	0.020	0.859	0.078
	AC$^+$ (mm^2/kPa)	294	0.0003	0.161	**0.006**	0.122	98	0.0003	0.250	**0.023**	0.102
	β$^+$	294	0.00007	0.021	0.729	0.077	98	−0.001	−0.226	**0.036**	0.135
	Ep$^+$ (kPa)	294	−0.002	−0.055	0.341	0.121	98	−0.009	−0.222	**0.038**	0.152
	PWVβ$^+$ (m/s)	294	−0.0001	−0.059	0.312	0.099	98	−0.0002	−0.204	0.054	0.164
	cSBP$^+$ (mm Hg)	296	−0.010	−0.179	**<0.001**	0.433	99	−0.0004	−0.011	0.916	0.168
	aPWV$^+$ (m/s)	296	−0.0003	−0.130	**0.005**	0.455	99	0.0001	0.081	0.407	0.270
Training intensity (MET-hours-index)	cIMT* (mm)	295	0.0002	0.139	**0.016**	0.150	98	0.00006	0.085	0.460	0.070
	Carotid diameter* (mm)	293	0.001	0.089	0.132	0.102	97	0.001	0.089	0.409	0.186
	cIDR*	293	0.00002	0.053	0.369	0.020	97	−0.000003	−0.018	0.878	0.078
	AC$^+$ (mm^2/kPa)	293	0.002	0.177	**0.002**	0.128	97	0.001	0.158	0.169	0.070
	β$^+$	293	−0.0003	−0.013	0.823	0.077	97	−0.002	−0.089	0.432	0.099
	Ep$^+$ (kPa)	293	−0.018	−0.064	0.262	0.122	97	−0.017	−0.078	0.482	0.116
	PWVβ$^+$ (m/s)	293	−0.001	−0.064	0.269	0.100	97	−0.001	−0.058	0.598	0.132
	cSBP$^+$ (mm Hg)	295	−0.029	−0.082	0.082	0.409	98	0.008	0.043	0.686	0.170
	aPWV$^+$ (m/s)	295	−0.001	−0.057	0.214	0.441	98	0.001	0.117	0.244	0.276

cIMT, carotid intima-media thickness; cIDR, carotid intima-media thickness:carotid diameter-ratio; AC, arterial compliance; β, beta stiffness index; Ep, elastic modulus; PWVβ, carotid pulse wave velocity; cSBP, central systolic blood pressure; aPWV, aortic pulse wave velocity; MET, metabolic equivalent. Significant results are marked in bold.

**Adjusted for age, sex, body surface area, training years, and bSBP.*

$^+$Adjusted for age, sex, body surface area, and training years.

individuals with an extremely high exercise load can be reversed to the approximate levels of inactive individuals, thus, high and intensive exercise can be of disadvantage (9).

Arem et al. (40) described a dose-response relationship of exercise levels per week and mortality risk, analogous to Eijsvogels et al. (9), which depicted a reduction in the mortality risk with higher exercise volume but a revision of the trend and increase of mortality risk at an exercise volume of ≥ 75 MET h/week. In our study, higher training duration and intensity was both related to a thicker cIMT, independent of the number of years the participants have been exercising. Furthermore, concerning training duration, both Q4 and Q5 showed significantly higher cIMT compared to Q1 and Q2. This means that children and adolescents who trained at least 8 h per week in a sports club had thicker cIMT. Concerning training intensity, a gradual increase from Q2 (> 48.45 MET-hours-index) was observed and children and adolescents in Q5 (>99 MET h/week) showed a significantly greater wall thickness compared to Q2 (Δ0.018 mm) and Q3 (Δ0.024 mm) compared to their peers.

cIMT is only a surrogate for subclinical vascular changes but independently associated with a higher risk for cardiovascular mortality (41). This emphasizes cIMT as an important parameter in assessing cardiovascular health, not only in patients but also in asymptomatic subjects – starting to screen them at a young age to prevent cardiovascular events in the future. Regarding our cohort, all participants are children and adolescents who are actively training in sports club activities. Therefore, our study participants are different from other studies investigating vascular changes in patients or inactive subjects and, therefore, cannot be compared to these studies. Although the study design does not allow to assume a dose-response relationship between training load and cIMT in our study collective, the results show that intensive exercise is associated with a thicker vessel wall.

During intensive exercise, the carotid artery diameter increases steadily by 6%, while after exercise the diameter decreases by 3% below the baseline level. One hour after exercise, the diameter is again 3% above the baseline level (42). Therefore, our result that higher carotid diameter was observed with higher training intensity might suggest that this increase in carotid diameter persists after exercise. Thijssen et al. (43) observed a similar diameter of the carotid artery in young adults after an 8-week cycling training. Rowley et al. (44) compared three arteries between upper limb athletes, lower limb athletes, and controls. They found that the effect of exercise on the vessel diameter was locally situated at the exercising limb. They observed larger brachial artery diameter in upper limb athletes, larger superficial femoral artery diameter in lower limb athletes, and similar carotid artery diameter in upper and lower limb athletes compared with controls. To what extent the results of Rowley et al. (44) can already be observed in childhood and adolescence should be clarified.

Also, we observed no correlation between the cIDR and training frequency and training intensity in our active children and adolescents. In contrast to our study results, Rowley et al.

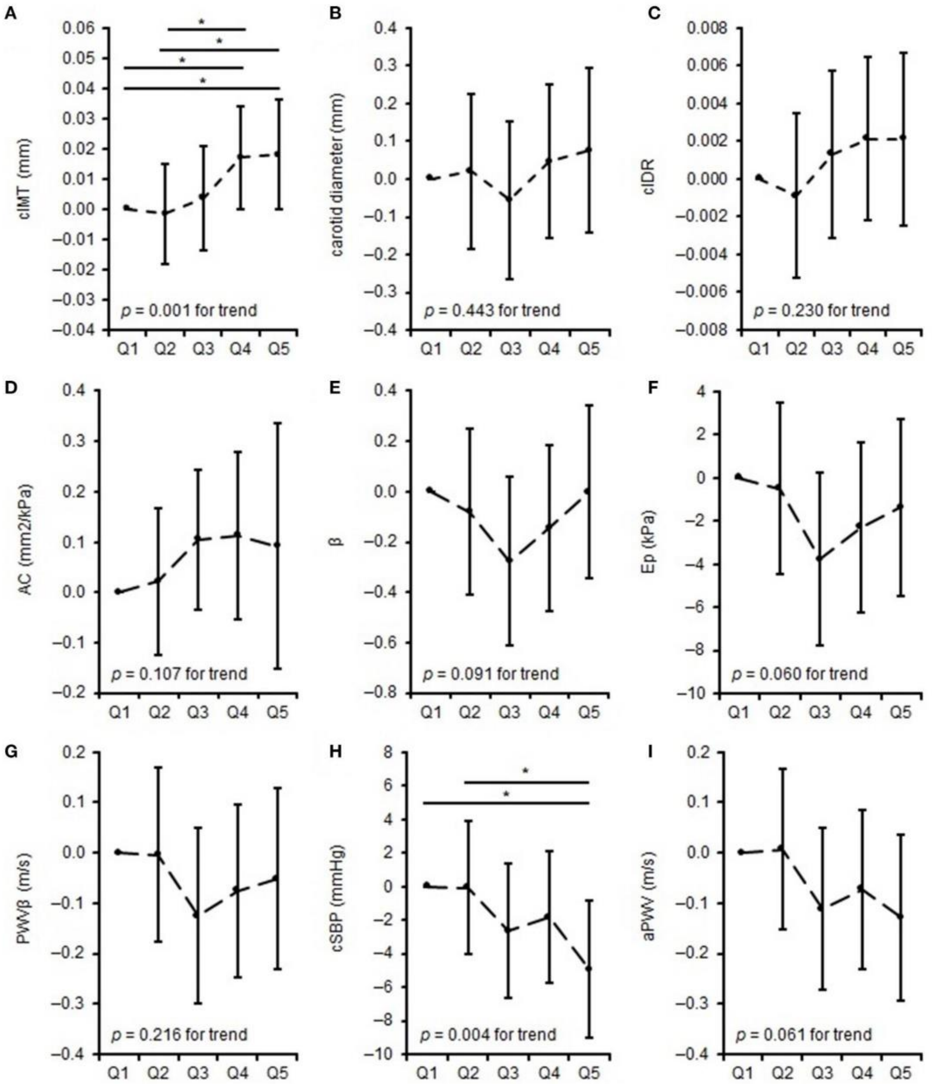

FIGURE 1 | Differences in measures of vascular properties: mean difference to the lowest quintile of training duration. **(A–C)** represent differences in carotid arterial structure, **(D)** represents differences in carotid arterial elasticity, **(E–G)** represents differences in carotid arterial stiffness, **(H,I)** represents differences in central vascular function across quintiles of training duration. *when $p < 0.05$. cIMT, carotid intima-media thickness; cIDR, carotid intima-media thickness:carotid diameter-ratio; AC, arterial compliance; β, beta stiffness index; Ep, elastic modulus; PWVβ, carotid pulse wave velocity; cSBP, central systolic blood pressure; aPWV, aortic pulse wave velocity.

(44) reported significantly lower wall-to-lumen ratio of carotid, superficial femoral, and brachial arteries in upper and lower limb athletes than controls. Furthermore, Thijssen et al. (43) observed a significant reduction of the wall-to-lumen ratio of the carotid and superficial femoral artery after an 8-week cycling training. In our study, we did not differentiate between local physiological stimuli of different types of sports, e. g. measurement of vascular properties at the superficial femoral artery in soccer players or measurement of vascular properties at the brachial artery in rowers. It is conceivable that the chronic exertion of endurance or strength sports or sports that involved the upper or lower body may lead to a different form

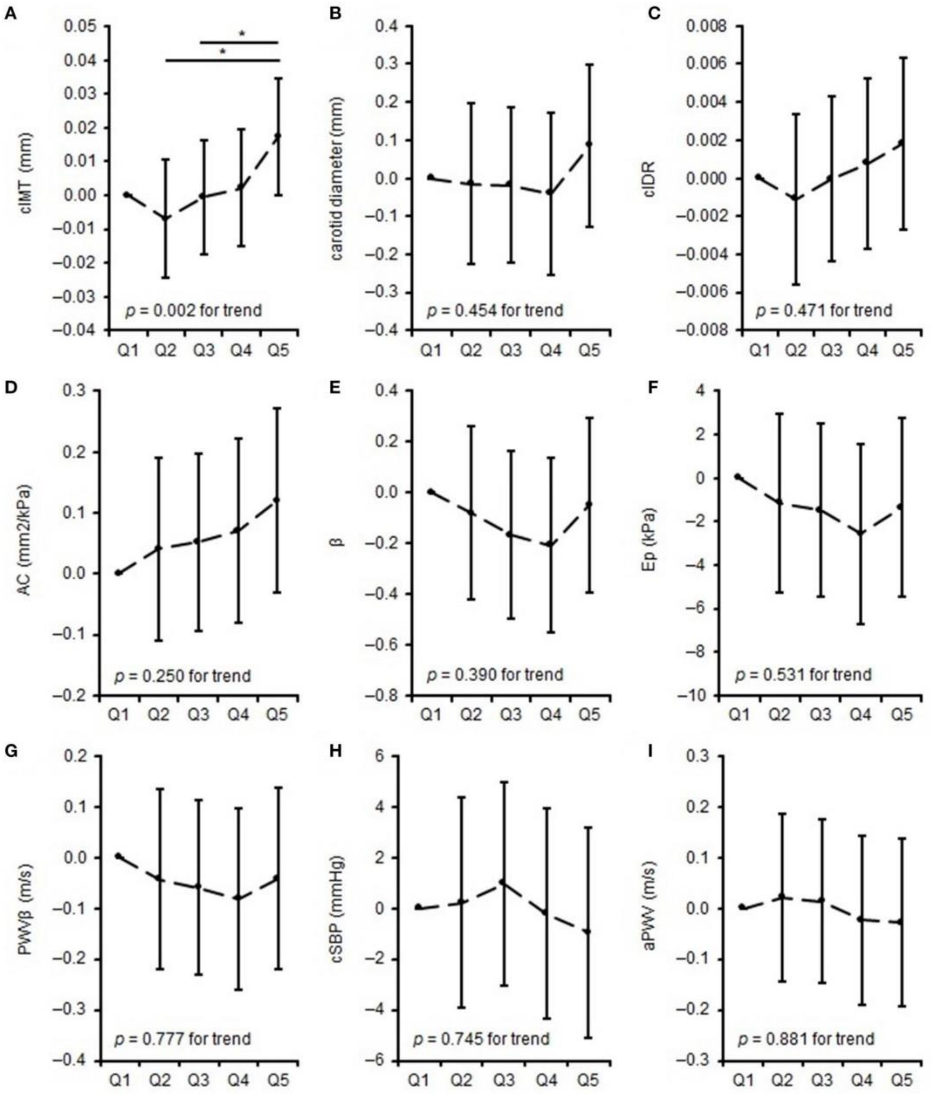

FIGURE 2 | Differences in measures of vascular properties: mean difference to the lowest quintile of training intensity. **(A–C)** represent differences in carotid arterial structure, **(D)** represents differences in carotid arterial elasticity, **(E–G)** represents differences in carotid arterial stiffness, **(H,I)** represents differences in central vascular function across quintiles of training intensity. *when $p < 0.05$. cIMT, carotid intima-media thickness; cIDR, carotid intima-media thickness:carotid diameter-ratio; AC, arterial compliance; β, beta stiffness index; Ep, elastic modulus; PWVβ, carotid pulse wave velocity; cSBP, central systolic blood pressure; aPWV, aortic pulse wave velocity.

of adaptation of the vascular system to exercise at a young age. Furthermore, the type of sport's influence on the adaptation of structural properties is also of interest in this context. However, it was not possible in our study to investigate differences in vascular properties between types of sport because children and adolescents from many different types of sports participated in the study.

The adaptation of vascular properties as a result of exercise is related to the increase in blood flow, the associated increase in shear stress and influence of vasodilators (NO, eNOS), synthesized by endothelial cells (45, 46). Therefore, in our study, we cannot determine to what extent other factors, such as metabolic or vasoactive substances, change vascular properties at a young age as a result of exercise.

Carotid and Central Vascular Function

Children and adolescents in our study have a higher carotid arterial elasticity (AC, 1.55 mm^2/kPa in boys and 1.45 mm^2/kPa in girls) and lower carotid arterial stiffness (Ep, 37.4 kPa in boys and 38.2 kPa in girls; β, 3.18 in boys and 3.28 in girls; PWVβ, 3.60 m/s in boys and 3.65 m/s girls) than the cohort of Weberruß et al. (22), which consisted of healthy children assessed in a school setting (AC, 1.2 mm^2/kPa in boys and girls; Ep, 46.6 kPa in boys and 44.9 kPa in girls; β, 3.9 in boys and 3.8 in girls; PWVβ, 4.0 m/s in boys and girls). Even though our study collective is ∼2 years older, these comparisons support the evidence that physical activity is favorably associated with carotid arterial elasticity in children and adolescents (14). In contrast, our study participants showed a higher cSBP (105.9 mmHg in boys, 102.5 mmHg in girls) and a higher aPWV (4.93 m/s in boys, 4.74 m/s in girls) than Elmenhorst et al. (34) (cSBP, 100.76 mmHg boys and 100.5 mmHg in girls; aPWV, 4.7 m/s in boys and 4.6 m/s in girls). Differences in elasticity between proximal and distal arteries might be explained by the fact that vascular smooth muscle cells along the arterial tree are derived from different sources of progenitor cells (47). For example, the vascular smooth muscle cells in the CCA develop from the neural crest, while the vascular smooth muscle cells in the dorsal aorta have their embryonic origin from somites (47, 48). These differences do not only occur between different vessels but even between individual segments of a single vessel (47). However, when comparing aPWV and PWVβ, it should be considered that aPWV was measured oscillometrically at the brachial artery and calculated by the three-level algorithm, and PWVβ was measured by ultrasound at the carotid artery. Therefore, it is important to consider the localization of the measurement (central or carotid) when interpreting arterial stiffness.

In our study collective, we observed better carotid arterial elasticity correlated with both higher training duration and intensity. Overall, we could not find an association between parameters of carotid arterial function and training duration or intensity. However, the results of the quintile analyses of training duration suggest that β, Ep, and PWVβ follow an approximately U-shaped pattern. The parameters decreased between Q1 and Q3, which indicated a reduction in carotid arterial stiffness, whereas from Q3 to Q5, parameters increased again, which implied higher carotid arterial stiffness. In Q5, the carotid arterial stiffness parameters were below (Ep and PWVβ) or at a comparable level (β) to Q1, which led to the conclusion that carotid arterial stiffness of children and adolescents in Q5 was improved (Ep and PWVβ) or comparable (β) with that of children and adolescents in Q1.

A comparison of previous studies on the association between arterial stiffness and physical activity or exercise in children and adolescents revealed a heterogeneous pattern. Ried-Larsen et al. (49) observed lower values of carotid Young's elastic modulus and stiffness index with higher moderate-to-vigorous physical activity. Weberruß et al. (22) assessed carotid arterial stiffness using the same protocol and equipment in $n = 870$ children and adolescents. In a sub-sample of $n = 697$ subjects (376 girls), cardiorespiratory fitness was significantly associated with carotid arterial stiffness parameters. No significant associations were obtained for muscular strength. In a one-way variance analysis, very fit boys and girls (>80th percentile for cardiorespiratory fitness) had significantly lower carotid arterial stiffness parameters compared with low fit subjects (<20th percentile). In contrast, other studies could not find a link between carotid arterial stiffness and physical activity in children and adolescents (14). Also, Demirel et al. (12), who compared adolescent wrestlers with controls, did not find significant differences in carotid arterial stiffness parameters. In contrast, in physically active adults, higher carotid arterial stiffness was observed in swimmers than cyclists, lower arterial stiffness in cyclists than controls, and similar carotid arterial stiffness between swimmers and controls (50). Therefore, carotid arterial stiffness also seems to be influenced by the type of sport performed.

We observed a lower cSBP and aPWV and thus a better central vascular function associated with a higher training duration but not with training intensity. Furthermore, the lower bSBP in Q5 of training duration compared to Q1 und Q2 confirms the findings of the linear regression analyses and depicts improved central arterial function in children and adolescents of very high training load. There was a tendency but not a significant difference between quintiles of training duration and aPWV, with the curve of aPWV being very similar to the curve of bSBP.

Previous studies on the relationship between physical activity in everyday life and central arterial stiffness have found little to no correlation in children and adolescents (14). However, the fact that targeted physical activity can affect central arterial stiffness is indicated by a comparison of extremely frequent physical activity with controls. Although Bauer et al. (51) observed lower cSBP in elite handball players, Vlachopoulos et al. (5) found higher cSBP and aPWV in marathon runners, both studies compared to controls.

However, it seems that the type of exercise plays a decisive role in this context. D'Andrea et al. (6) observed 190 strength athletes, 220 endurance athletes, and 240 controls. They found better aortic distensibility in endurance athletes compared to strength athletes and controls but higher aortic stiffness in strength athletes than endurance athletes and controls. Furthermore, they concluded that training duration and endurance training have a significant positive impact on aortic distensibility. In contrast, training duration and strength training have a significant negative impact on aortic stiffness. Also, a targeted 12-week strength training in powerlifting athletes increased cSBP (52). In addition to the type of training and the training duration, the training intensity also influences vascular function. Vlachopoulos et al. (5) found that the intensity of exercise in marathon running is related to a significantly higher aPWV, corrected for mean pressure.

Differences Between Boys and Girls

We observed sex-specific differences in vascular properties, although boys and girls were of similar age. Boys showed thicker cIMT, larger carotid diameter and cIDR, higher central hemodynamics and carotid arterial elasticity compared to girls, which is in contrast to a German reference cohort (22). While the positive relationship between AC and training duration was confirmed in both girls and boys according to the overall analysis, better carotid arterial elasticity in correlation with training intensity was only observed in boys. Controversially, only girls showed lower carotid arterial stiffness (β and Ep) associated with higher training duration, while only boys showed improved central hemodynamics associated with higher training duration. The positive association between cIMT and training duration and intensity was also confirmed only in boys.

Sex differences are, in general, difficult to interpret according to chronological age, as vascular properties aligned with the maturation stage (53). In boys, puberty generally starts later than in girls and in young athletes later than in their peers (54, 55). Even if an exact determination of the maturity status was not obtained, it can be assumed that a large majority of the included subjects are currently in the puberty phase due to the medium age of 14.0 ± 1.94 years. In our study setting, it was not possible to determine the puberty status based on the Tanner stages, because the study participants visited our outpatient clinic for a fee-based sports medical examination and not for study purposes only.

Differences in hormone levels between boys and girls might explain the differences in vascular properties. Testosterone is released in boys during puberty and increases the activation of the sympathetic nervous system and renin-angiotensin system, which is associated with increased SBP (56, 57). Furthermore, higher testosterone levels are associated with higher arterial stiffness and left ventricular mass, which in itself is associated with higher cIMT (58–60). In contrast, estradiol and progesterone levels, which are higher in girls compared to boys, have a cardioprotective effect (61–64).

Future Directions

It is necessary to clarify whether the relationship between cIMT and higher training load manifests itself with the continuation of training activities or whether the adolescent body adapts to the training loads and the vascular properties normalize as a result. In addition, the relationship between vascular and cardiac properties in young active subjects should be further clarified to preclude possible adverse effects of thickened cIMT with higher training load on cardiac structure and function. Furthermore, measuring cardiovascular endpoints is difficult in this age group. Therefore, cohort studies should investigate whether alterations in vascular properties that already occur in youth as a result of exercise lead to a higher risk of cardiovascular disease and mortality in the future. Moreover, vascular properties should be compared between different sports to investigate the effects of sport-dependent training loads. In this context, not only the vascular properties of the CCA should be investigated, but also the properties of the femoral and brachial artery, since different sports affect different areas of the body. Future studies should also investigate whether the sex differences in the relationship between vascular properties and exercise duration and intensity have a hormonal explanation.

Limitations

Some limitations affect our study results. Owing to the cross-sectional design, it is not possible to make a causal statement regarding the cause-and-effect relationship between the duration and intensity of exercise and vascular properties. Therefore, we will investigate this aspect in a further longitudinal study, paying attention to whether a permanently high level of activity leads to changes in vascular properties (15). Our study collective consisted of children and young people who were regularly active in sports clubs and did not include a control group with inactive children and adolescents. Therefore, it is not possible to assess whether active and inactive children and adolescents differ in vascular properties. We assessed weekly training duration and intensity using a questionnaire. Compared with accelerometers, questionnaires measure subjective and not objective activities. Therefore, the validity of the data obtained by questionnaires depends on the respondents' ability to remember and the accuracy of the information provided. In order to collect the exercise behavior as exactly as possible, the questionnaire was explained in detail and help was offered. A further limitation is the missing assessment of the maturity status because it is known that maturity status influences the vascular properties of children and adolescents (53).

Furthermore, we did not measure biochemical parameters, such as nitric oxide, that have been reported to influence the relationship between exercise and vascular properties (65). The regression models of carotid arterial function revealed a poor model fit. In contrast, the regression models of the cIMT with about 20% and the regression models of central arterial function with more than 40% (total and boys) revealed an acceptable model fit. Independently of our association analyses, other factors, which we have not recorded, exist which forecast the carotid arterial function of active children and adolescents. Therefore, future studies should include parameters such as maturity status and biochemical markers.

CONCLUSION

We studied for the first time the association between training duration and intensity and vascular properties and sex-specific differences in these associations in a study collective of active children and adolescents. The novelty findings of our study are a negative association between training load and cIMT, but better carotid arterial elasticity in physically active children and adolescents. Furthermore, central hemodynamics were improved with higher training duration, whereas girls showed lower carotid arterial stiffness. Therefore, we assume a muscular and also functional adaptation as a result of intensive exercise. In future, children and adolescents with extremely high training loads should be regularly examined with regard to their vascular properties in order to detect possible negative and persistent effects of competitive sports on vascular health at an early stage.

DATA AVAILABILITY STATEMENT

The datasets analyzed within the study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Technical University of Munich. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

LB, HW, TS, and RO-F designed the study. LB and TE performed the data collection. LB performed the data analysis and drafted the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.618294/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

4 Discussion

The four articles of this dissertation provide insights into how physical activity is related to vascular structure and function in children and adolescents.

The review in article 1 showed that, in general, physical activity and physical fitness are favorably associated with vascular structure and function in children and adolescents. In addition, exercise interventions were found to be suitable for improving vascular structure and function in children and adolescents with impaired vascular properties due to underlying cardiovascular or metabolic disease. The review confirmed that there is currently limited evidence on how vascular structure and function behave in children and adolescents who exercise above average.

The comparison of young athletes with a reference population in article 3 has shown that young athletes have higher cIMT and cIDR, higher carotid elasticity and lower carotid stiffness, and higher cSBP and aPWV compared with appropriate reference values. Furthermore, it was shown that young male athletes have higher cIMT, carotid diameter, cSBP, and aPWV with concurrent higher brachial SBP, training duration, and physical performance than young female athletes.

Finally, in article 4, only children and adolescents active in sports clubs were considered, and their vascular properties were analyzed concerning training duration and intensity. The study has shown that active boys have higher cIMT, carotid diameter, carotid elasticity, cSBP, and aPWV than active girls. Table 3 summarizes the associations of training duration and intensity with the vascular parameters for the overall study population and separated for girls and boys.

Table 3. Association of training duration and intensity with vascular properties

	Overall		Girls		Boys	
	duration	**intensity**	**duration**	**intensity**	**duration**	**intensity**
cIMT	↑	↑	-	-	↑	↑
Carotid diameter	-	↑	-	-	-	-
cIDR	-	-	-	-	-	-
AC	↑	↑	↑	-	↑	↑
β	-	-	↓	-	-	-
Ep	-	-	↓	-	-	-
PWVβ	-	-	-	-	-	-
cSBP	↓	-	-	-	↓	-
aPWV	↓	-	-	-	↓	-

cIMT, carotid intima-media thickness; cIDR, carotid intima-media thickness:carotid diameter-ratio; AC, arterial compliance; β, beta stiffness index; Ep, elastic modulus; PWVβ, carotid pulse wave velocity; cSBP, central systolic blood pressure; aPWV, aortic pulse wave velocity.

Active children and adolescents with extremely high training duration (> 8h/week) had higher cIMT but lower cSBP than those with low training duration. Active children and adolescents with extremely high training intensity (> 99 MET-hours-index) had higher cIMT than those with low intensity.

4.1 Carotid structure and function

In the overall consideration of all articles, this dissertation showed better carotid function (higher elasticity and lower stiffness) with higher physical activity and exercise. The comparison of the vascular properties of young athletes with age- and sex-specific reference values has shown that young athletes had better carotid elasticity (AC) and lower carotid stiffness (β, Ep, PWVβ) (145). Thus, the result of the study by Ried-Larsen et al. (150) can be confirmed, where lower carotid stiffness was observed mainly in the highest quintile of MVPA. Although the regression analyses showed an association between training duration and intensity with carotid elasticity, the quintile analyses did not detect differences in carotid elasticity and stiffness between the quintiles of training duration and intensity (146). This discrepancy in the results could be explained by the fact that Ried-Larsen et al. (150) and Baumgartner et al. (145) compared two groups that were very different in their activity levels. This was not the case in Baumgartner et al. (146) because even Q1 still included active children and adolescents in sports clubs.

A more detailed analysis of the included studies in the review revealed an age effect (143). Whereas studies in children found no association between physical activity and carotid stiffness (126, 151), studies in adolescents showed better carotid elasticity and, thus, lower carotid stiffness with higher physical activity (152, 153). Training experience of almost 3.5 years suggests that active adolescents have been participating in sports since childhood (145, 146). Because the performance load in young athletes increases with age, the results of this dissertation suggest that carotid function adapts positively with growing age and the corresponding increase in performance level in boys and girls. This may indicate that the ‘athlete's artery’, described by Thijssen et al. (89) as having, among other things, improved elasticity and reduced stiffness of conduit arteries, develops at a young age.

An essential finding of this dissertation is the increased cIMT at higher levels of exercise. 40.8% of young athletes presented cIMT > 75th percentile. The higher cIMT in young athletes compared with a reference collective and the higher cIMT with increasing training duration and intensity indicates a remodeling of arteries already in adolescence (145, 146). Because the diameter of the CCA did not differ from the reference population, but cIDR was increased, the results indicate that there is a ‘pediatric athlete’s artery’, characterized by a thickening of the vessel wall (see Figure 8).

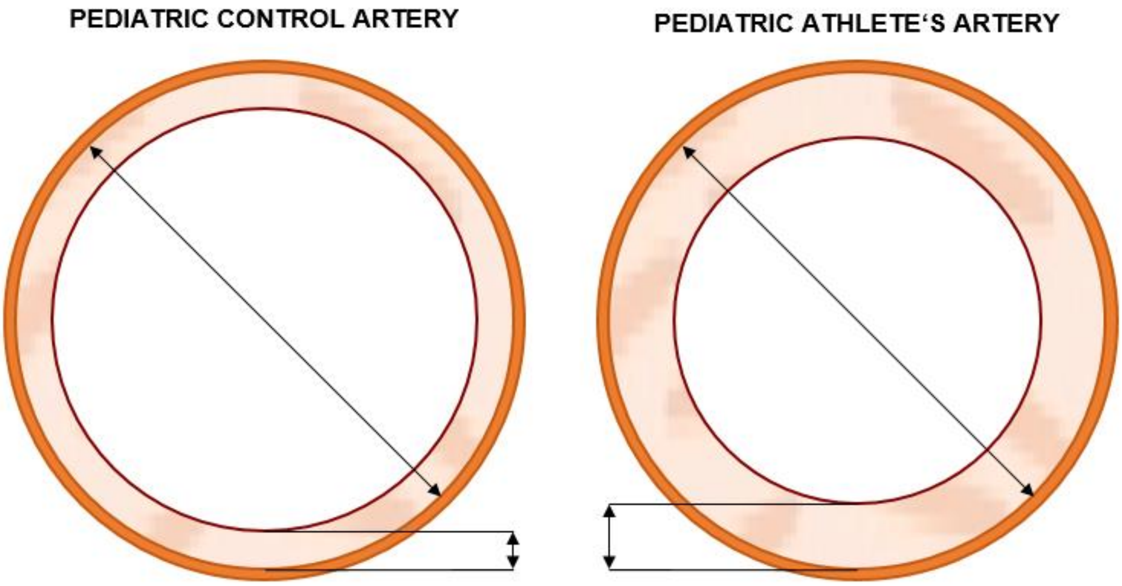

Figure 8. Representation of the ‘pediatric athlete’s artery’ of the carotid artery, characterized by an increased cIMT, unmodified diameter, and increased cIDR compared to controls. Created based on the results of this dissertation and following Green et al. (95)

However, according to the concept of the athlete’s artery, one would expect reduced cIMT at higher levels of exercise (95). There is broad evidence that cIMT increases in pediatric patients suffering from obesity, type 1 diabetes, metabolic syndrome, and hypertension (154-156). In healthy study populations, health-related physical fitness but not physical activity has a relevant relationship with cIMT (143). However, exercise seems to be an appropriate intervention to reduce elevated cIMT levels to an average level in pediatric risk groups (157). Although cIMT appears slightly higher in low physically active children and adolescents than in moderately to highly active children and adolescents in this dissertation, no clear significant difference was detected. Thus, there is no evidence that the cIMT becomes thinner with increasing physical activity. Instead, it appears that the cIMT stabilizes at an average level. In highly active children and adolescents (> 8h training/week), cIMT can rise to levels that would be rather expected in children and adolescents with underlying cardiovascular or metabolic diseases. Summarizing these dissertation results graphically, a reverse J-shaped curve can be identified, similar to Eijsvogels et al. (158) on the dose-response association between physical activity and cardiovascular health outcomes (see Figure 9).

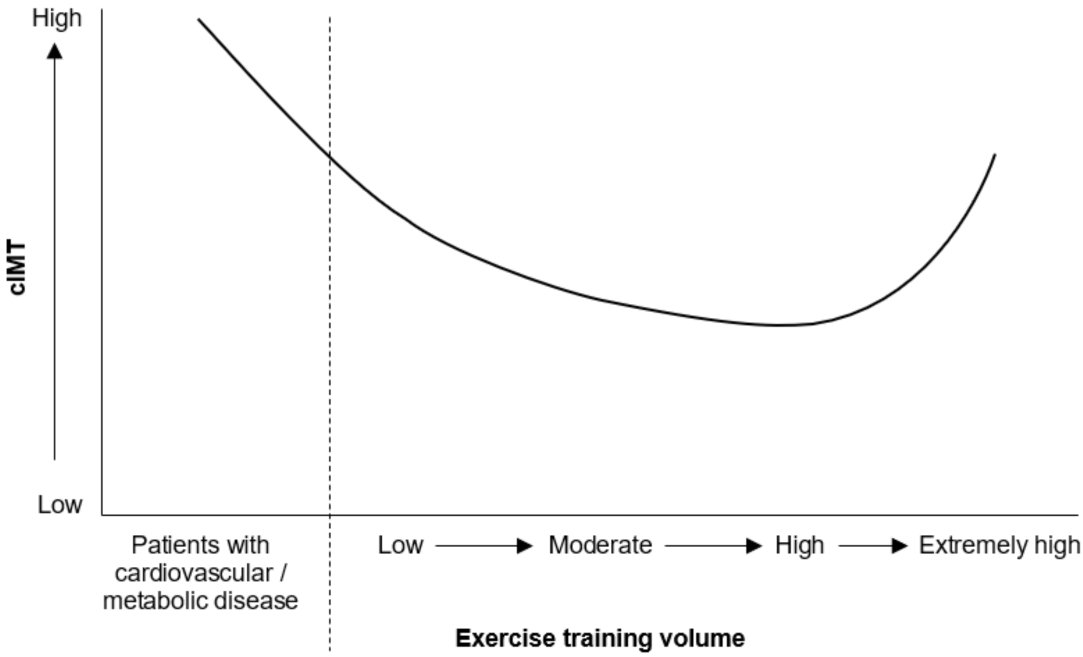

Figure 9. Reverse J-shaped curve of the association between physical activity and cIMT. Created based on the results of this dissertation and following Eijsvogels et al. (158)

However, it cannot be concluded from the results of this dissertation that exercising children and adolescents also have a higher cardiovascular risk due to increased cIMT. It is assumed that the increased cardiovascular risk derived from increased cIMT is mainly due to the thickening of the intima layer in the vessel wall. Since the process of atherosclerosis occurs predominantly in the intimal layer of the arterial wall, however, thickening is also more likely to occur there. However, B-mode ultrasound cannot measure the tunica intima and media separately. The study subjects of this dissertation showed better vascular elasticity despite the higher cIMT. This implies that higher exercise volumes in children and adolescents are associated with improved endothelial function. However, because thickening of the intimal layer in the vessel wall would simultaneously be expected to result in decreased vascular elasticity and thus increased arterial stiffness at the CCA, the increased cIMT with increased exercise volume could argue for thickening of the media layer, triggered by the proliferation of VSMC in the tunica media. However, this dissertation cannot provide scientific evidence for this theory of vascular adaptation to exercise in children and adolescents by a response of VSMC. Nevertheless, considering cIMT as an isolated parameter for vascular adaptation and physical activity at this young age would be misleading. Nonetheless, the question arises if there can be a ‘too much exercise’ in young athletes.

4.2 Central arterial stiffness

The review conducted within the framework of the dissertation showed that physical activity is associated with lower central arterial stiffness in population-based studies. Although there is broad evidence for the health-promoting effect of physical activity on arterial stiffness in children and adolescents, the recent systematic review and meta-analysis by Lona et al. (3) showed that only two studies had examined this association in methodologically well-conducted studies to date.

The favorable association between physical activity and arterial stiffness was observed when only children and adolescents were considered who were exercising in sports clubs (aged between 8 and 17 years, no minimum level of physical activity). Even in this group, a linear reduction in central arterial stiffness was found with increased weekly training duration (146). However, this positive effect is not evident when considering young athletes alone (aged between 12 and 17 years, at least 6h per week of physical activity in competitive sports) – they showed increased central arterial stiffness compared to a reference collective (145). Interestingly, in a subsequent analysis of the data set of Baumgartner et al. (146) (data not shown), the results revealed that the collective of physically active children and adolescents – like the young athletes – also showed higher central stiffness when vascular parameters were compared with the reference collective of Weberruß et al. (138). This means that both studied collectives of this dissertation showed higher central arterial stiffness than the reference collective of Weberruß et al. (138) with the same standard operating procedure. However, lower arterial stiffness was observed simultaneously with higher training duration. Therefore, it is questionable whether the study collective of the MuCAYA study differed from the reference collective in other, so far unknown, parameters. Furthermore, training intensity seems to play less of a role than the weekly training duration regarding central vascular function.

Given that increased arterial stiffness predicts all-cause and cardiovascular mortality, the raised central arterial stiffness in young athletes is worrying but consistent with studies in adult athletes (9, 114, 159). The animal study by Rubies et al. (160) also suggests that especially intensive exercise compared to moderate exercise leads to increased aortic stiffness and, thus, vascular remodeling. In addition to fibrosis of the tunica media, they observed abnormalities of the elastic laminae, thickened intramyocardial arteries, and stiffening of VSMC as a result of intensive exercise. Interestingly, the remodeling induced by training did not remove after short-term detraining.

Vlachopoulos et al. (9) explained the increased aPWV in adult/mature marathon runners with the increased stroke volume. The consequently increased aortic distension exerted such a tremendous pressure on the vessel wall that it led to mechanical fatigue and, therefore, to increased arterial stiffness. The higher cSBP and aPWV in young athletes might indicate a link between arterial stiffness and cardiac adaptation to exercise in the young. Characteristics of cardiac adaptation to exercise are increased cardiac output, increased end-diastolic dimensions of the right and left ventricle (LV) (LV), LV hypertrophy, increased LV mass, and increased volume of the left atrium (161). It is known that increased arterial stiffness correlates with higher central blood pressure and is associated with higher LV strain and relative wall thickness (159, 162, 163). In athletes, LV hypertrophy is defined as LV wall thickness > 12mm. Such pronounced LV hypertrophy is less present in young athletes than in adult athletes. Out of 720 adolescent athletes, only 0.4% showed LV wall thickness > 12mm. Nevertheless, adolescent athletes show significantly higher LV wall thickness than controls (11).

Changes in LV dimensions were also demonstrated in the MuCAYA study, whose data were the basis for articles 3 and 4 of this dissertation. Weberruß et al. (149) evaluated the echocardiographic data of the MuCAYA study in their publication. In a collective of young competitive athletes (age 7-18 years, minimum 3h training per week), they observed increased LV internal diameter in systole but not in diastole, interventricular septal thickness, and LV posterior wall thickness in diastole compared to appropriate reference values. Regression analyses showed increased LV internal diameter in systole and diastole, intraventricular septal thickness, and LV mass relative to body surface area with increased training intensity and $VO2_{peak}$. 54.1% of males and 45.4% of females presented eccentric hypertrophy, and 5.5% of males and 8.2% of females showed concentric hypertrophy, independent of the type of sport. Since no altered LV systolic and diastolic function was observed at the same time, the authors concluded that functional cardiac adaptations already occur in the collective of young competitive athletes.

Summing up the results of this dissertation and Weberruß et al. (149), the MuCAYA study showed altered LV dimensions and increased central arterial stiffness in exercising children and young adolescent athletes. However, it must be noted that although the study population was the same in all studies, the samples differed depending on age and training volume. Therefore, analyzing the relationship between cardiac and vascular parameters within a homogeneous sample would be appropriate. Because the MuCAYA study followed the children and adolescents for several years, cardiac and vascular parameters should also be analyzed longitudinally to identify whether increased central arterial stiffness predicted changes in LV dimensions and wall thickness or whether these changes in cardiovascular structure and function developed simultaneously.

4.3 Role of type of sport, puberty, and sex

The MuCAYA study recruited subjects via the pediatric sports medical outpatient department. The children and adolescents usually visited the outpatient department for a PPCS, which was required for their sports club or association. The pediatric sports medical outpatient department cooperated with various sports clubs and associations; therefore, the study population's composition strongly depended on these cooperations. This explains the large proportion of soccer players, almost 40%. Overall, the distribution of sports in the study population is unequal. The second most frequently played sport, volleyball, for example, only accounts for slightly less than 10%.

The overall analysis of all types of sports in this dissertation for the general statement of the association of physical activity and exercise with vascular properties in the context of cardiovascular risk assessment is reasonable. However, as described in the theoretical background of this dissertation, studies in adults have shown that different sports elicit different local physiological stimuli and, therefore, the adaptation of structural and functional vascular properties depends on the type of sports (endurance, strength, mixed) and the mainly trained limbs. Whether different types of sports lead to local vascular changes already in children and adolescents is not possible to prove within our setting due to the methods applied in this dissertation.

Most study participants in this dissertation were between 12 and 16 years old. Although pubertal status was not assessed in the MuCAYA study, it can be assumed that many study participants were in puberty. This starts at 8 to 13 years for girls and between 9 to 14 years for boys (164). Adolescence is an exceptionally hormonally demanding developmental phase, so it is essential to consider girls and boys separately in the context of vascular characteristics.

In this dissertation, boys presented higher cIMT, carotid diameter, cSBP, and aPWV (145, 146). Although some studies show no differences in cIMT between girls and boys (138, 165-167), other studies report higher cIMT in boys (168, 169). Doyon et al. (170) concluded that the difference between girls and boys in cIMT becomes apparent starting at age 15, and that boys show a higher cIMT with increasing age. The observation of the percentile curves by Drole Torkar et al. (169) also leads to the conclusion that the gap between girls and boys increases with age. Therefore, the results of this dissertation are consistent with the literature. According to Doyon et al. (170), one explanation for the sex differences in cIMT could be the tremendous increase in blood pressure, which coincides with the growth spurt in pubescent boys.

The observed higher carotid diameter in boys is in line with the literature (139, 171, 172). Sarkola et al. (171) show that although age significantly affects carotid diameter, the carotid diameter increases primarily in childhood and remains relatively constant between 10 and 18 years of age. Because carotid diameter in late childhood and adolescence depends mainly on SBP and body surface area, and in the evaluation of young athletes in this dissertation, both SBP and body surface area were increased in boys, the higher carotid diameter in boys may be explained by the increased SBP and body surface area. (171). Elmenhorst et al. (135) and Reusz et al. (173) demonstrated a steady increase in cSBP and aPWV during childhood and adolescence, with sex differences only becoming apparent after age 13. From this age onwards, cSBP and PWV increase more in boys than in girls, resulting in a significant difference. This age range also includes most of the study population in the MuCAYA study and explains the higher cSBP and aPWV in boys.

Sex-specific analyses explored differences between exercising boys and girls in the association of training duration or intensity and vascular parameters. While the results of the overall analysis regarding training duration (higher cIMT, better AC, lower cSBP, lower aPWV) were confirmed only in boys, girls presented better β and Ep. Interestingly, both boys and girls showed improved AC with higher training duration. Furthermore, only boys showed higher cIMT but better AC with higher training intensity (146).

One explanation for these differences might be the interplay of staggered onset of body change and sex-specific hormonal influences on vascular tone during puberty. Puberty usually begins later in boys than in girls, and the length growth characteristic of puberty peaks almost two years later in boys compared with girls (174). Therefore, the higher estradiol and progesterone levels in girls may explain the association of training duration and beta and Ep, as both hormones have a cardio-protective effect (175-178).

In addition, puberty begins later in exercising adolescents than in less active adolescents of the same age (179). A reasonable explanation for the sex differences in the relationship between training duration or intensity and vascular parameters cannot be provided due to the missing assessment of pubertal status and measurement of hormone levels.

4.4 Limitations

Some limitations restrict the significance of the results of this dissertation.

The data of vascular properties and physical activity were only evaluated in a cross-sectional design and, therefore, only allowed a conclusion about an association, but not regarding whether and to what extent physical activity influences vascular properties in young athletes. As part of the MuCAYA study, the data will also be analyzed longitudinally and published in a separate article. This article will examine whether a permanently high activity level leads to changes in vascular properties.

The sample composition depended mainly on which children and adolescents visited the sports medical outpatient department for children and adolescents during the study period to complete their annual PPCS. On the one side, this did not actively influence subject recruitment. On the other side, however, this resulted in an overrepresentation of some types of sports, such as soccer, and an underrepresentation of very endurance or strength-based sports. This also resulted in an unequal distribution of boys and girls.

Although the vascular properties of the young athletes were compared with a reference collective, which is equivalent to a comparison with a control group, the evaluation of the difference in vascular properties in distinct groups of training duration and intensity would have been more meaningful with the comparison with a control group. Unfortunately, this analysis was not possible with the reference collective because the MoMo-AFB was not used in this study.

The physical activity of the children and adolescents was recorded using the MoMo-AFB and, thus, a subjective measurement tool. The disadvantage of using questionnaires is that self-assessments are often subject to recall errors, as individuals may forget to mention certain activities or overestimate the time or frequency of their physical activity. Using the MoMo-AFB, this is particularly relevant, as children and adolescents have to recall their physical activity in sports clubs and recreational sports in the last 12 months. To avoid misunderstanding the questions and answering all of them, the participants were instructed in advance in detail and with the required objectivity of the researcher on how to fill out the questionnaire. A major limitation of using the MoMo-AFB is that the children's and adolescents' self-assessments are not objective and rely only on the individual's subjective perception of physical activity levels. These self-assessments are inherently subjective and prone to errors. The gold standard in measuring physical activity are the objective methods of direct observation, calorimetry, and the double-labeled water test, which can hardly be implemented in practice due to their outstanding effort. Nevertheless, other measurement methods, such as accelerometers, could have been used to record physical activity objectively. However, with such objective methods, it is hardly possible to survey the training duration and intensity in club sports over the whole year, because such accelerometers are usually worn on the hip for one week. In addition, the practical implementation of using accelerometers was not given, with more than 200 children and adolescents examined annually. Therefore, great care was taken to ensure that the children and adolescents received precise instructions on completing the MoMo-AFB. Questions were clarified in the presence of the children and adolescents, and the answers were checked.

The current gold standard for non-invasive assessment of arterial stiffness is cfPWV. In this context, the use of tonometry is the method that best estimates central pressure and wave reflection (180). In this dissertation, central arterial stiffness was measured using the oscillometric device Mobil-O-Graph® and CCA arterial stiffness was assessed by ultrasound. The Mobil-O-Graph® is a non-invasive measurement tool that calculates central arterial stiffness based on peripheral waveform measurement and using ARCSolver algorithm. Therefore, cSBP and aPWV were not directly measured. Nevertheless, it is a valid instrument for measuring central arterial stiffness in children and adolescents, as demonstrated by the validation study of Walser et al. (133).

In assessing arterial stiffness via ultrasound, the local stiffness is determined depending on the local blood pressure and diameter using B-mode (47). Furthermore, the local PWV via ultrasound is calculated from the time delay between two adjacent strain waveforms (181). Ultrasound thus allows an exact local measurement of arterial stiffness because it is not estimated via an algorithm like the measurement of arterial stiffness via oscillometry (132). A disadvantage of using ultrasound to measure vascular properties is examiner dependence. The accuracy and reliability of the results may depend on the skill and experience of the operator, which can vary widely. Therefore, assessing of arterial stiffness with ultrasound equipment requires a trained operator. To minimize this limitation, ultrasound examinations were performed by only one person. Intra-observer validity was evaluated in 20 subjects and showed a coefficient of variation $< 5\%$ for all ultrasound parameters. Inter-observer validity compared with the reference collectives also showed acceptable results (138, 139). Therefore the quality of the ultrasound data can be rated as good.

The interpretation of vascular characteristics in adolescence depends on the maturity level of girls and boys. During puberty, there is a significant increase in hormones such as estrogen and testosterone, which can affect arterial stiffness and wall thickness (169, 182). It should, therefore, only be performed by measuring pubertal status, e.g., with the Tanner Scale. Data collection was performed in an outpatient clinic for children and adolescents as part of the annual PPCS. Therefore, the studies in this dissertation were not only research activities but were integrated into the service of offering a PPCS and thus into the daily routine of the outpatient clinic. Since applying of the Tanner scale can lead to feelings of shame among children, adolescents, and their parents, and to prevent the service of PPCS is not perceived by the children and adolescents in the following years due to this, the application of the Tanner scale was renounced.

Biochemical parameters such as NO or endothelin-1 play an essential role concerning exercise and vascular stiffness. Because the results of this dissertation regarding vascular stiffness are contradictory at some points (lower stiffness at the CCA, higher stiffness at the aorta), the measurement of NO or endothelin-1 would have been helpful to assess better the regulation of vascular tone and blood flow in active children and adolescents.

5 Conclusion and future research perspectives

In conclusion, this dissertation supports the positive association of physical activity and exercise with better carotid elasticity and lower carotid stiffness in children and adolescents. However, pediatric athletes demonstrated higher central arterial stiffness and an increased cIMT, suggesting arterial thickening and remodeling already in adolescence. Therefore, the results of this dissertation show that there is a ‘pediatric athlete’s artery’ of the CCA, which is characterized by a higher cIMT and cIDR, higher carotid elasticity, and lower carotid stiffness.

The cIMT is increased in young athletes; 40.8% of young athletes showed cIMT > 75th percentile. The association between exercise and increased cIMT appears to exhibit a reverse J-shaped curve, indicating that there may be a point where ‘too much exercise’ could lead to an increased cardiovascular risk, especially in highly trained young athletes. This result is worrying because higher cIMT is an important risk factor for cardiovascular disease, and physical activity should positively affect vascular structure.

Here, the question arises: why did the MuCAYA study observe these results, and what explains the thickened cIMT? Is this a thickening in terms of a higher cardiovascular risk for young athletes or a temporary functional adaptation that regresses later in the athlete's career? Is the thickened cIMT explained by a greater proportion of VSMC in the tunica media and not by thickening of the tunica intima, as is causative for the development of atherosclerosis? Also, the findings regarding central arterial stiffness – higher cSBP and aPWV in young athletes – need to be clarified to exclude that the young athletes are at higher short- and long-term cardiovascular risk because of their increased training volume.

In this dissertation, the vascular parameters of the MuCAYA study were evaluated; the cardiac parameters were published separately by Weberruß et al. (149). The future task of the MuCAYA study is now to assess the vascular and cardiac parameters together. This should include a cross-sectional analysis of whether those children and adolescents with increased cIMT or central arterial stiffness also have distinctive features in cardiac characteristics (eccentric or concentric hypertrophy, changes in LV dimensions, and changes in LV systolic and diastolic function). Future research also needs to address the longitudinal changes in cardiac and vascular parameters in children and adolescents with different levels of physical activity and training duration. The MuCAYA study provides a unique opportunity to follow up on the study population for several years and determine the development of cardiovascular structure and function. This combined view of the cardiac and vascular systems should provide an understanding of the overall adaptation of the cardiovascular system to exercise in childhood and adolescence. Therefore, the children and adolescents in the MuCAYA study should continue to be examined annually.

The significance of the results of this dissertation is limited by the lack of pubertal status and blood parameters influenced by physical activity and exercise (e.g., NO, endothelin-1). Future studies should follow up on this and consider these parameters to better understand the underlying mechanism.

Additionally, considering the large proportion of soccer players in the study population, future research could investigate the local vascular adaptation to different types of sports and limb-specific training in children and adolescents. In addition to the distinction between types of sports, a differentiation between the sports disciplines ‘skill’, ‘power’, ‘mixed’, and ‘endurance’ according to Pelliccia et al. (183) or dynamic and static sports according to Mitchell et al. (184) is recommended. In this context, not only the CCA should be selected as a point of the investigation, but also, for example, the brachial artery or femoral artery, to investigate local differences in addition to sport-specific differences.

Finally, more research is needed to determine the optimal exercise volume and intensity for different types of sports in children and adolescents to promote cardiovascular health benefits while avoiding adverse effects. By increasing our knowledge in this area, we can develop appropriate recommendations for physical activity and exercise in different groups of children and adolescents to promote cardiovascular health and prevent future cardiovascular disease.

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